A DESCRIPTIVE STUDY OF MORPHOEA WITH CLINICO-PATHOLOGICAL CORRELATION

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CERTIFICATE

This is to certify that this dissertation entitled **'A DESCRIPTIVE STUDY OF MORPHOEA WITH CLINICO-PATHOLOGICAL CORRELATION'** submitted by **Dr. ANUJ SAIGAL** to The Tamil Nadu Dr. M.G.R. Medical University, Chennai is in partial fulfillment of the requirement for the award of M.D. [DERMATO VENEREO LEPROLOGY] and is a bonafide research work carried out by him under direct supervision and guidance. This work has not previously formed the basis for the award of any degree or diploma.

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DECLARATION

I, **Dr. ANUJ SAIGAL** solemnly declare that the dissertation titled '**A DESCRIPTIVE STUDY OF MORPHOEA WITH CLINICO-PATHOLOGICAL CORRELATION'** is a bonafide work done by me at Government Rajaji Hospital during 2010 – 2012 under the guidance and supervision of **Prof. Dr. A.S. Krishnaram M.D., D.D.,** Professor and Head of the Department of Dermatology, Madurai Medical College, Madurai.

I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree and diploma to any university, board either in India or abroad.

The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree in Dermatology, Venereology and Leprology (BRANCH –XII A).**

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CONTENTS

INTRODUCTION

Morphoea is an uncommon benign fibrosing disease which shows involvement of dermis, subcutaneous fat and underlying tissues, more prevalent in females, and is a separate disorder from systemic sclerosis as there is no internal organ involvement.

Morphoea causes fibrosis of all mesoderm derived tissues and rarely, the central nervous system [CNS]. Linear, generalized, and pansclerotic types are associated with morbid features like contractures, facial disfigurement, distress, arthralgia and CNS involvement.

The pathogenesis of morphoea is still an enigma, but is proposed to be started by injury to the vessels that results in increased collagen synthesis and diminished collagen destruction. There are interesting serological associations with morphoea also. Various other systemic and cutaneous diseases have also been found to be associated with morphoea.

This disease often progresses for several years and then regresses even without treatment although various modalities of treatment have been tried in the past.

REVIEW OF LITERATURE

SYNONYMS

Localized scleroderma, Circumscribed scleroderma, Scleroderma en coup de sabre

HISTORICAL ASPECTS

The word morphoea was first used by Erasmus Wilson to describe this disease as he felt that the areas were vestiges of true leprosy[1]. Morphoea has been derived from 'morpheus' who in Greek tradition is considered as god of dreams with the capability to acquire any human form and appear in dreams.

The term 'sclerodermie' was coined in 1847 by the French physician, Gintrac[2].

Thomas Addison came up with the first detailed report on morphoea, who differentiated a ''true keloid'' from a ''keloid of Alibert.' The entity described by Alibert is now called as a keloid[3]. Matsui[4] described the typical histopathological changes of scleroderma in 1924. O'Leary and Nomland[5] elaborated the distinctive features of systemic sclerosis versus morphoea in an extensive clinical study in 1930.

DEFINITION

Morphoea is a localized form of scleroderma with increased collagen deposition leading to sclerosis of the dermis and underlying tissues[6]. It is a disorder of unknown cause with many clinical types and lack of systemic involvement thereby differentiating it from systemic sclerosis[7].

CLASSIFICATION OF MORPHOEA

Schachter[8] in 1989 subdivided localized scleroderma into

1) Morphoea- Limited (Plaque or Guttate), Generalised and others (subcutaneous, nodular).
2) Linear scleroderma- Linear or en coup de sabre. Since this scheme proved to be inconclusive, another classification was proposed by Peterson et al[9] in 1995 which divided morphoea into five main types

1) PLAQUE MORPHOEA

Morphoea en plaque

Guttate morphoea

Atrophoderma of Pasini and Pierini

Keloid morphoea (nodular morphoea)

[Lichen sclerosus et atrophicus {LSA}]

2) **GENERALIZED MORPHOEA**

3) **BULLOUS MORPHOEA**

4) **LINEAR MORPHOEA**

Linear morphoea

En coup de sabre (ECDS)

Progressive hemifacial atrophy

5) **DEEP MORPHOEA**

Subcutaneous morphoea

Eosinophilic fasciitis

Morphoea profunda

Disabling pansclerotic morphoea of childhood

This classification is questioned now because of two main reasons. Firstly, it has many entities which are not universally considered under morphoea like LSA, Pasini and Pierini's atrophoderma and eosinophilic fasciitis. Secondly, it does not include those patients who have more than one morphological type of morphoea and can be considered under an entity, 'mixed' variant.

Recently, a new classification for localized scleroderma was proposed at consensus conference at Padua, Italy in 2004, which included circumscribed

morphoea, linear morphoea, pansclerotic morphoea, generalized morphoea and mixed morphoea[10].

Types	Subtypes	Details
Circumscribed morphoea	Superficial	Single or multiple, oval or round indurated areas involving epidermis and dermis often with a surrounding liliac ring.
	Deep	Single or multiple oval or round deeply indurated areas involving subcutaneous (SC) tissue (upto muscle in few cases); may spare the skin above.
Linear morphoea	Trunk/limb subtype	Indurated areas in a linear fashion involving the dermis and SC tissue (may involve upto the level of muscle and bone)
	Head subtype	En coup de sabre Induration in a linear fashion of the face and scalp (can include muscle, bone and CNS) Parry Romberg syndrome (PRS) Involvement of one side of the face with overlying mobile skin.
Generalized morphoea		Individual indurated plaques, 4 or more in number, of size more than 3 cm each and involving two of seven sites including head and neck, front of trunk, back of trunk, right upper limb, left upper limb, right lower limb, left lower limb.

Pansclerotic morphoea		Circumferential involvement of limbs upto the level of bones. Other body areas may also be affected.
Mixed variant morphoea		Variant with 2 or more of the above mentioned subtypes. Sequence is consistent with predominant representation in the patient like (pansclerotic-circumscribed).

EPIDEMIOLOGY OF MORPHOEA

Morphoea can affect all ages though it is most commonly seen in the 20- 40 years age group, but the disease commences before the age of 10 years in 15 % of cases according to a study conducted by Christianson et al[11] on 235 cases. The extremes of age were 1 year and 76 years in this study[11].

The prevalence of the disease also increases with age[12]. It is undoubtedly more common in females with ratio approximately being 3:1 in most studies[11,12] with the exception of linear morphoea which has no gender preference . In a study done by Peterson et al[12] in Olmsted county between 1960-1993 on 82 cases showed the incidence rate as 27 per million population. According to the same study[12], 56% of patients had plaque type morphoea, 20% linear, 13% generalized and 11% deep morphoea whereas study conducted by Christianson et al[11] showed more number of cases with linear morphoea as compared to plaque type.

A worldwide study of 750 children with juvenile localized scleroderma also reported more percentage of linear lesions than plaques[13]. Also, Christianson's study[11] showed that linear lesions appeared before the age of 10 years in 20% and prior to the age of 40 in 75% but plaque lesions appeared later in life, 10% were seen prior to the age of 10 years and 75% becoming evident between the ages of 20 and 50. The results from these studies show that linear morphoea is more commonly seen in children as compared to adults.

Morphoea is more prevalent in Caucasians and Asians and it has been reported to be rare in black people like African Americans[14,15]. The disease is active for a span of 3 to 6 years on an average[15,16]. Relapses are more commonly seen in patients with generalized morphoea, linear morphoea and deep morphoea whereas circumscribed morphoea has the shortest course[16].

AETIOLOGY

1) TRAUMA

Trauma can be considered as a triggering factor for morphoea and may precede the onset of the disease by many months[17]. Two case reports suggesting that trauma causes an isomorphic response and appearance of new typical lesions in known cases of morphoea have been published[18]. The mechanism is still unknown but local production and dysregulation of inflammatory mediators including fibrogenic cytokines such as transforming growth factor (TGF-β) have been proposed to cause excessive synthesis of collagen[19]. Trauma has been reported as a precipitating factor in approximately 13% of the children examined under two large studies of almost 900 cases[13, 20]. The study conducted by Christianson et al[11] reported 14 cases out of 191 with trauma as the preceding factor.

2) IMMOBILIZATION

Immobilization is another aetiological factor proposed for morphoea. It has been reported that it causes dermal fibroblasts activation, thereby releasing inflammatory cells and ultimately causes fibrosis[21]. 2 cases have been reported till date which developed morphoea after immobilization[21].

3) VACCINATIONS AND INJECTIONS

Vaccinations such as B.C.G , D.P.T, MMR , tetanus and hepatitis B have been reported to cause morphoea[22,23,24]. The underlying pathogenesis is still not well understood; it has been proposed that injection trauma causes endothelial injury and hypoxia of tissues which leads on to morphoea. Another hypothesis proposed is that vaccines induce an immune response against various antigens (specific as well as nonspecific). Finally, wound healing releases various cytokines and growth factors which might also predispose to trauma induced morphoea. Till date, 8 cases of vaccination induced morphoea have been reported[25].

Other injections like vitamin K, vitamin B12 and progesterone have also been reported as causative factors for morphoea[22,26]. The vehicle used, the preservative, and hypersensitivity have been implicated as the various reasons behind this[26]. There have been many case reports of morphoea developing after vitamin K injections (Texier disease) and it has been observed that it takes 1 month to almost 2 years for the morphoea like changes to occur[27]. High dosing is another factor which was seen in most of the cases. These sclerodermoid plaques were called as ‘cowboy’s belt with revolver’ in one recent case report[28].

4) RADIOTHERAPY

` Morphoea has been reported to occur following radiotherapy, most commonly seen in women with breast carcinoma[29]. The incidence has been reported to be 1 in 500 cases[29]. The morphoea lesions usually develop around the irradiation port but some cases show involvement of areas beyond these sites or may extend to any other distal site[29]. The time duration after which the patient develops such lesions ranges from less than 1 year to 32 years after irradiation[29]. The pathogenesis proposed involves either activation of fibroblasts or self antigen presentation resulting in tissue damage[25]. Another case with post-fluoroscopy appearance of morphoea was also reported[30].

5) SURGICAL OPERATIONS

Surgical operations have been known to precede morphoea. Surgeries like rhinoplasty and AV fistula formation have been reported to cause morphoea. Another case report stated the development of morphoea post-laparotomy[22].

6) HORMONAL FACTORS

There are case reports where pregnancy has been reported to exacerbate lesions of morphoea[31]. A recent case report published in 2011 described pregnancy exacerbation of en coup de sabre and post

partum development of rheumatoid arthritis[31]. The mechanism proposed for this association deals with increase in the number of T regulatory cells in pregnancy which causes increased synthesis of TGF-β which is a known potent pro-fibrogenic mediator in scleroderma. A higher incidence of morphoea has also been seen around menarche. Parathormone has also been linked with morphoea by causing calcium deposition in soft tissues[14] and subtotal parathyroidectomy has been used as the treatment but no real proof has been offered to support this. Leriche and co-workers[32] observed 13 patients with generalized scleroderma for 2 to 5 years after a subtotal parathyroidectomy with 90% improvement.

7) INFECTIONS

Borrelial infection has also been proposed to play a role in morphoea. After reviewing various studies on borrelial infection in morphoea, it was concluded that about 51% of patients were reported to have been infected with Borrelia infection[25]. Even, histopathological specimens of morphoea patients have revealed borrelial DNA in few cases[33]. On the other hand, various other studies have reported contradicting findings stating that there is no association between morphoea and Borrelia infection[34].

The probable reason for almost all the reports coming from Europe might be the difference in strains seen in Europe in comparision to United States of America (B.afzelii or B.garinii vs B.burgdorferi sensu stricto, respectively)[25]. Reports proposing Cytomegalovirus as another aetiologic agent have also been published[35]. Morphoea has been reported to follow infections like varicella, herpes zoster, toxoplasmosis and hepatitis C as well[22,36,37].

8) GENETIC FACTORS

Genetic role for morphoea is still unclear but a familial incidence has been noted and there have been reports of localized scleroderma occurring in monozygotic twins[38]. There has been no significant HLA association reported with morphoea till date[39]. Organ specific autoantibodies have also shown a rise in some patients and relatives[22].

9) ROLE OF DRUGS

There have been reports of morphoea occuring after intake of various drugs such as D-penicillamine, bromocriptine, hydroxytryptophan, carbidopa, valproic acid, pentazocine, docetaxel, paclitaxel, bleomycin and after melphalan limb perfusion[22]. Other drugs like bisoprolol, peplomycin and balicatib have also been implicated in development of morphoea[40]. The onset of morphoea after starting the drug ranges from 1

month to 30 months[40]. Withdrawal of drugs may or may not result in clearance of lesions.

Kraigher et al[41] documented blaschkoid unilateral generalized morphoea after intake of ibuprofen which showed relief after stopping the drug. The pathogenesis mainly revolves around production of autoantibodies by these drugs that affect the microvasculature and ultimately forming morphoea plaques[25].

10) OTHER MISCELLANEOUS CAUSES

Other triggering factors include mechanical compression from clothing, pigmented purpuric dermatosis like lichen aureus[42]. Even exposure to epoxy resins, vinyl chloride, organic solvents and pesticides, silicon implants etc have been reported to produce scleroderma like changes.

PATHOGENESIS

An increase in extracellular matrix and collagen deposition mainly accounts for the pathogenesis of morphoea. The exact mechanism for this still remains an enigma. Pathogenesis can be understood under the following headings

a) VASCULAR INJURY

According to the vascular theory, morphoea starts with an injury to the vessels which may be caused by an infection or antibodies to endothelial cells[43]. This is further supported by the biopsy changes seen in the early morphoea lesions.

b) ADHESION MOLECULES EXPRESSION AND PRO FIBROTIC CYTOKINES SYNTHESIS

The injury to the endothelium leads to cytokine release which causes increased intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin expression[44]. These molecules via T cells release other cytokines which cause fibrosis like IL- 4, IL-6 and TGF-β. This leads to accumulation of eosinophils, helper T cells, and macrophages. These cells are thought to present self antigens to the immune system of the body and thereby release autoantibodies.

Various chemokines such as CCL and CXCL8 have also been proposed to be involved in the pathogenesis of fibrosis[45]. Other cytokines like IL-2 receptor, CD 23, CD30 and B-cell activating factor also play a role[22]. The stage of active inflammation and sclerosis has shown the presence of CD 34 and dermal dendrocytes. Sclerodermatous skin has been reported to show mast cells in the early stages[46].

c) OVERABUNDANCE OF COLLAGEN DEPOSITION

Upregulation of TGF-β leads to collagen, fibronectin, and proteoglycan deposition and it also diminishes collagen degradation by causing a decline in the levels of matrix metalloproteinases[45,47]. This variation in the amount of collagen deposition and collagen degradation is the proposed mechanism of the fibrosis seen in morphoea[47]. Antibodies to MMP's may also play a role in the inhibition of collagen degradation. The accumulation of myofibroblasts by GTPase Rac 1 also plays a role in the pathogenesis[48]. Insulin-like growth factor may also contribute to the development of morphoea by accumulating fibroblasts and increasing collagen and extracellular matrix deposition[49].

Gene array analyses showed 4 separate gene signatures and were classified as inflammatory, limited, proliferative and normal-like. The inflammatory signature was seen in patients with morphoea. Other signatures were seen in systemic sclerosis[50].

ROLE OF MICROCHIMERISM

There has been a recent advancement in the understanding of morphoea and scleroderma with microchimerism being proposed to play a role. Various PCR studies (realtime and nested) have shown the presence of chimeric cells in morphoea patients. Although the exact cause still remains an enigma, further research in this area may elucidate the exact pathogenesis and role of epithelial-derived chimeric cells in morphoea[51].

ROLE OF AUTOANTIBODIES

The association of morphoea with autoimmune diseases ranges from 2% to 30% in various case reports published till now. Diseases such as Graves disease, vitiligo, type 1 diabetes mellitus, chronic GVHD, Idiopathic thrombocytopenic purpura and ulcerative colitis have been reported to coexist[13,52]. However, the prevalence of autoimmune disease observed in general public is lower than these values. The reported prevalence of positive ANA titers in morphoea patients ranges from 20% to 80%[20,52,53,54]. High values of antihistone antibodies, single stranded antibody, RA factor and homogenous ANA have also been reported in morphoea patients[54].

However, childhood-onset morphoea shows more prevalence of antihistone antibodies[53] whereas anti single stranded antibodies are seen in generalised and linear morphoea. High titres of ANA have been reported to occur in juvenile patients with linear morphoea and patients with generalised morphoea[54].

The titers have not shown any significant correlation with the course or severity of disease[26,52,53,54]. Antitopoisomerase II alpha antibody is also found in morphoea especially in generalized morphoea patients[55]. B-cell activating factor (BCAF) can also show a rise in morphoea[22]. Diminished levels of anti RNP antibodies and antiendothelial cell antibodies have been seen in morphoea patients[22,43,56]. Also, anticardiolipin, antinucleosome

antibodies, fibrillin 1 antibodies have also been found in localized scleroderma patients[22]. Cytotoxicity due to antibodies or complement activation may have a role in pathogenesis of morphoea[25].

CLINICAL PRESENTATION

Morphoea starts with an active stage presenting as erythematous to violaceous patches or plaques. As the lesions progress, the center becomes white and sclerotic which is surrounded by a characteristic 'liliac ring' forming the border. After the active stage, sclerotic plaques are seen. Some cases show plaques with postinflammatory hyperpigmentation. The excessive collagen production damages hair follicles and adnexal structures thereby forming hairless plaques which are anhidrotic[25]. Raynaud's phenomenon is not seen in most cases just like sclerodactyly which are features of systemic sclerosis. Very few cases develop systemic sclerosis later in life[7]. Another characterstic feature is that face and the acral areas are typically spared except in some variants of linear morphoea[15].

1) CIRCUMSCRIBED MORPHOEA (morphoea en plaque)

Circumscribed morphoea is the commonest type of morphoea reported in adults. This diagnosis is entertained when there are less than 3 discrete indurated plaques mostly seen over the trunk[13,26,52]. It presents as round or oval circumscribed indurated areas with a central waxy, ivory colour

surrounded by a violaceous halo. The size may vary from less than 1 cm to 30 cm[15]. It mainly involves the dermis with involvement of the panniculus in few cases[57].

This type is further classified as superficial or deep. The superficial subtype is more commonly seen and the extent of involvement is till epidermis and dermis. Early lesions show an inflammatory or liliac border. The deep subtype (previously called SUBCUTANEOUS MORPHOEA or MORPHOEA PROFUNDA) involves the dermis and SC tissues and may extend till the muscle beneath. The skin above may be normal, atrophic, or indurated and is attached to the deeper tissues beneath which accounts for the characteristic 'bound down' feeling. Hypoaesthesia may be seen. Obscure abdominal pain and migraine may be associated[11].

Some patients develop lesions in the pressure associated areas as if they are koebnerizing. Women commonly show lesions over breasts but nipples are not involved[25]. The natural history is towards resolution and softening of lesions over a span of 3 to 5 years but these patients are predisposed to develop new lesions in the future[13].

OTHER RELATED VARIANTS

a) GUTTATE MORPHOEA

Peterson et al[9] classified guttate morphoea under plaque morphoea. Guttate morphoea most commonly occurs on the upper aspect of the trunk as multiple oval lesions that are 2 to 10 mms in diameter. The disease starts with a mild erythema which proceeds to minimal induration and pigmentation abnormalities[9]. It has been proposed that LSA (white spot disease) and guttate morphoea are one and same and these two diseases have a similar pathogenesis.

b) NODULAR / KELOIDAL MORPHOEA

Keloidal morphoea (nodular morphoea) is described as presence of keloid resembling nodules along with typical morphoea lesions. The nodules may be confluent or isolated[9]. In 1894, Unna denominated this condition 'keloid-like scleroderma'[58]. It has been reported in both localized and systemic scleroderma but is more commonly seen in systemic sclerosis[59]. However, both keloidal and nodular morphoea are considered as one but few reports have documented differences between the two entities. Barzilai et al[60] stated that the term keloidal morphoea includes those cases which have both clinical and histological findings consistent with keloid whereas nodular scleroderma is used for cases which have histological features comparable

with scleroderma. It is common in females seen in the 30 to 50 years of age group. The dermatohistopathologic examination may show 1) keloid findings 2) scleroderma findings 3) keloid and scleroderma findings[61]. The cause of nodular morphoea is not well known. Acid-fast bacilli and hepatitis C virus are the infectious aetiologies proposed for nodular morphoea[62]. A role of organic solvents has also been reported. Cutaneous inflammation can also contribute in keloid prone individuals.

Acrokeratoelastoidosis has been reported to be associated with nodular morphoea[63].

c) ATROPHODERMA OF PASINI AND PIERINI

The clinical appearance of Pasini and Pierini's atrophoderma has been compared to 'footprints in the snow' or 'Swiss cheese-like' pattern. Morphologically, oval or round, soft, blue to pigmented atrophic areas with 'cliff-drop' borders[64] mostly seen over trunk. Since pronounced inflammatory or sclerotic changes are absent, this entity is often considered "burnt-out morphoea." It can occur alone or with other morphoea subtypes elsewhere on the skin[9]. Lesions are chronic in nature and are present for 10 to 20 years. Many authors have considered it as a variant of morphoea[64].

The various synonyms used previously for atrophoderma like morphoea plana atrophica, morphoea with unusual degree of atrophy further supports that atrophoderma was considered under morphoea spectrum in

various case reports[64]. The similarities and differences between the two are as follows[65,66,67]

SIMILARITIES WITH MORPHOEA	DIFFERENCES FROM MORPHOEA
Similar to the late stage of morphoea clinically and histologically.	Earlier onset and a longer course and rare spontaneous involution.
Indurated areas similar to morphoea present within lesions.	Characterstic cliff-drop border which is absent in morphoea.
Coexistence of both diseases in the same patient.	Atrophy is followed by induration but opposite in morphoea.
May progress to systemic scleroderma.	Appendageal structures remain intact in atrophoderma unlike morphoea.

d) BULLOUS MORPHOEA

Peterson et al[9] classified bullous morphoea as one of the types but bullous lesions can occur in any type of morphoea. The cause for bullous lesions relates to dilatation of lymphatics and release of eosinophil mediators like major basic protein[68]. Another school of thought is that patients who have associated LSA develop blisters. The level of bulla is subepidermal.

2) LINEAR MORPHOEA

Linear morphoea is most commonly seen in children, although it is seen in adults as well[13,20,52]. It follows the lines of Blaschko and mosaicism has been the proposed mechanism for this[69]. There have been reports stating that bilateral involvement in linear morphoea of children ranges from 5 to

25%[13, 26]. Patients usually complain of pain, arthralgia or oedema before the onset of the lesions[11]. Clinically, one or more lesions in a linear fashion with an inconspicuous liliac ring are seen and show involvement upto the underlying bone thereby resulting in deformities, contractures, and severe limb atrophy[9]. Linear morphoea involves lower limbs more commonly as compared to the upper limbs. Homolateral lesions involving limbs of one side of the body have also been documented. Rarely one half of the body may be affected. The lesions are seen along the limb or around the trunk, but ainhum like lesions have also been reported[70]. Linear morphoea is associated with high titres of ANA usually. Hypertrichosis, melorheostosis and dystrophic calcinosis cutis are few asssociations of linear morphoea[22]. Keloidal morphoea was also seen in a linear fashion in one report[71]. Linear morphoea of lower limbs is more commonly associated with spina bifida occulta[11]. The subtypes of linear morphoea are en coup de sabre, Parry Romberg syndrome and linear limb involvement[25].

a) **EN COUP DE SABRE (FRONTOPARIETAL LINEAR MORPHOEA)**

This entity has been so named as the morphology of the lesion simulates the depression caused by a duelling stroke from a sword[57]. It usually affects the forehead. Associated eye and CNS involvement is also seen[25]. En coup de sabre is almost always unilateral, but rarely bilateral cases have been reported[72]. The disease initiates with contraction and firmness of

the overlying skin which then progresses to the formation of an ivory coloured sclerotic plaque lesion with increased pigmentation at the borders. Ultimately, a groove in a linear fashion is seen on the frontoparietal area which extends into the scalp and results in the formation of a linear alopecic patch. This depression may involve the cheek, nose and upper lip extending into mouth and gingiva[73]. In some patients, involvement upto chin and neck may be seen[22]. There may be invovement of jaw which may lead to dental abnormalities. Hemiatrophy of the tongue and hemifacial atrophy may be visible in less than a year[22]. Rarely, frontoparietal lesions may be trilinear and may follow lines of Blaschko[74].

Bony abnormalities of skull and EEG changes may be present[22]. Neurological abnormalities have been reported with ECDS[75]. Eye involvement is also commonly seen[76]. External ocular muscle involvement, enophthalmos, fundus changes and vasculitis are some of the ocular complications[76]. Iris atrophy on the medial side and loss of upper eyelashes were also reported in a patient which exactly followed the line of cutaneous lesion[77]. Heterochromia of the iris may also be associated[78]. Eyelid oedema in one eye has been reported as the presenting lesion in a case report[79].

b) **PROGRESSIVE HEMIFACIAL ATROPHY (PARRY-ROMBERG SYNDROME)**

This disease presents as atrophy of the face on one side. It involves the skin and tissue below the forehead but the overlying skin is either not involved or minimally affected. It is treated as a severe form of en coup de sabre by some authors and hence it is considered as a variant of the head subtype of linear morphoea. The associated disorders such as neurological abnormalities, teeth and eye changes are also reported in Parry Romberg syndrome thereby further supporting the above proposition[80].

Less than 10% cases report atrophy of the upper extremity on the same side. Unilateral hemiatrophy of full body has also been reported. Tollefson et al[81] did a study on 54 patients with ECDS and progressive hemifacial atrophy and found out that these are two times more commonly seen in females as compared to males. Tollefson et al[81] also concluded by considering ECDS and progressive hemifacial atrophy as variants of same disorder just like other authors.

3) PANSCLEROTIC MORPHOEA

It is an uncommon, severe, mutilating form of morphoea involving the dermis, fat, fascia, muscle and even bone, usually starting before the age of 14 years, although adult-onset cases have been reported[82]. It may develop from linear morphoea. Superficial and deep sclerosis mainly affects the trunk,

limbs, scalp and face but the fingertips and toes are spared[22]. There may be a claw deformity of the hands and patients may walk on tiptoe because of contracture of the Achilles tendons[22]. Arthralgia and stiffness may be seen initially and patient might have intense pain because of cutaneous nerves involvement[83]. Raynaud's phenomenon is absent, but oesophagus, lungs and teeth have been involved in a few cases. Flexion contractures, osteoporosis and other bone changes are pretty common. The electromyogram and histology of muscle may be abnormal, but creatine phosphokinase is under normal limits. Elevation of ESR, hypergammaglobulinaemia and eosinophilia are frequent[22]. The disease is progressive showing poor respose to treatment and occasionally fatal. These cases, especially those with resultant chronic wounds, are at increased risk of squamous cell carcinoma (SCC) of the skin[25]. Wollina et al[84] estimated that 6.7% of patients with pansclerotic morphoea develop SCC every year.

4) GENERALISED MORPHOEA

It is characterized by indurated areas of the skin which begin as individual plaques, 4 or more in number of size greater than 3 cms. Later on, they merge and affect atleast two out of seven sites including head & neck, right lower limb, left lower limb, right upper limb, left upper limb, anterior trunk and posterior trunk[57].

Similar lesions affecting just one side of the body have also been reported and are considered as an extreme variant which has its onset during childhood[85].

According to the study conducted by Christianson et al[11], generalized morphoea is most commonly seen in the 30 to 40 years age group. Also, approximately eighty percent of cases have their age of onset between 11 and 50 years of age[12]. It is more commonly seen in the females. The lesions have a predilection for the trunk and newer lesions develop over time along with increase in size of the existing plaques. Usually, there is no systemic involvement[22]. Mechanical compression is considered as one of the aetiological factors. Expressionless face with shiny, brown and indurated skin is seen. Mouth opening may be restricted[22] and thorax abnormalities may lead to difficulty in breathing as well. Involvement of intercostal muscles has been reported to cause death from respiratory failure[86]. Raynaud's phenomenon may be present but is not seen in all cases. Bullous, keloidal or nodular[59] type may coexist with generalized morphoea. Acral myofibromas may occur in few cases[87]. Contracture of joints, hardening of limb and soreness may be the presenting complaints in acute phase of the disease. Joint pains were reported in 50% of cases[12]. Chronic lesions for more than 20 years may lead to the development of squamous cell carcinoma in few cases and calcinosis cutis may be another association[88]. Sick sinus syndrome, necrotizing vasculitis,

polymyositis, biliary cirrhosis and fasciitis are some of the other associations[22]. The disease usually improves after 3 to 5 years but may last for longer periods.

5) MIXED MORPHOEA

Approximately 15% of patients have more than one type of morphoea and they are classified under mixed morphoea[13,52]. The sequence, in brackets is consistent with predominant presentation in a case {like mixed morphoea (pansclerotic-circumscribed)}[57].

EXTRACUTANEOUS INVOLVEMENT AND ASSOCIATIONS

Morphoea is not just a cutaneous disease and it has various extracutaneous associations. These are reported to be evident in almost 20% of the cases and multiple associations are seen in 4% of cases. A recent study of morphoea in 750 children[13] from Europe showed that almost 25% had extracutaneous manifestations with joint manifestations in 47%, CNS in 17%, vascular in 9% and eye, gastrointestinal, respiratory, kidney and cardiac abnormalities being reported in few cases. CNS involvement consisted of seizures, vasculitis, neuropathy, headache and neuroimaging changes. Eye involvement showed episcleritis, uveitis, glaucoma, xerophthalmia and papilledema. Reflux disease was the most common gastrointestinal manifestation. Autoantibodies like ANA and rheumatoid factor showed higher values in those cases which had some associated disease.

Another study conducted by Guariso et al[89] showed esophageal involvement in 57% of cases. In the study conducted by Christianson et al[11], few patients gave history of Raynaud's phenomenon in one hand and intermittent recurrent colicky abdominal pain. Spina bifida, presence of six lumbar vertebrae, transverse arch prolongation, scoliosis, lumbar segements pain, rudimentary rib, kyphosis, cervical rib, torticollis, atrophic clavicle, lack of pectoralis muscle, pelvic contraction, short ulna and deformities of acral parts were other associations[11]. Morphoea has also been reported to coexist with carpal tunnel syndrome, nephritis, primary biliary cirrhosis, myasthenia gravis[22]. Myopathy, osteomyelitis[90], rheumatoid arthritis[20], crohn's disease[20], hashimoto's thyroiditis[91], celiac disease[20], B cell lymphoma[92] are other associated diseases.

ASSOCIATED SKIN CONDITIONS

Morphoea has been reported to occur with warty, vascular or pigmented nevi, café-au-lait macules, alopecia areata, generalised ichthyosis, dystrophic nails, hirsutism[22], vitiligo[93], discoid lupus erythematosus[94], mixed connective tissue disease[95], eosinophilic fasciitis, becker's melanosis[96], sclerotic panatrophy with disseminated granuloma annulare[22], systemic lupus erythematosus[97], dermatomyositis[22], pemphigus[22], localized bullous pemphigoid with subcorneal pustulosis[22], elastosis perforans serpiginosa[22], lichen sclerosus et atrophicus[98], psoriasis[20], oral submucous fibrosis,

pigmented purpuric dermatosis and lichen planus[98]. Systemic sclerosis patients can have coexisting plaques of morphoea in few cases[99]. There have been reports of morphoea progressing to systemic sclerosis in the past[11,14]. Chronic and long standing lesions can undergo malignant transformation like squamous cell carcinoma[84] and in sometimes in patients managed with azathioprine[100].

INVESTIGATIONS

BLOOD INVESTIGATIONS

Anaemia may be seen in morphoea and a case of linear scleroderma was reported with autoimmune haemolytic anaemia as well[101]. Blood eosinophilia (> 300 cells/mm^3 or more than 6%) has been reported in 7 % to 50% of cases with morphoea with study conducted by Marzano et al[16] on 239 cases showing 7 % of the patients having eosinophilia whereas the studies conducted by Christen-Zaech et al[20] on 136 children and Zulian et al[13] on 750 children showing 18 % of cases with raised levels of eosinophils in blood. Blood eosinophilia was seen in 50% of patients in a study conducted by Falanga et al[102]. Eosinophilia was more commonly seen in patients with linear and generalised morphoea[20,102]. The levels of eosinophilia correlated with the disease activity with declining levels coinciding with decrease in activity of skin lesions[102]. ESR and CRP may also be raised[13,16]. Zulian et al[13] documented 22.2% of linear morphoea children with raised ESR.

Thrombocytopenia was also seen in 2 cases[103]. Hypergammaglobulinemia with elevated polyclonal IgM and IgG occurs in almost 50% of patients with severe skin disease and is more common during clinical progression[6]. Complement levels are usually normal, but a C2 complement deficiency has been described to coexist with en coup de sabre.

AUTOANTIBODIES

Several auto-antibodies are found in morphoea[57] including antinuclear antibodies (46-80%), anti-ss DNA (50%) and antihistone antibodies (47%). Anti ss DNA antibodies are commonly seen in cases with generalized morphoea (75%) and linear morphoea (50%). Patients with muscle involvement showed increased levels of these antibodies than patients without any muscle involvement. Disease activity can be predicted by the levels of anti ss DNA in a patient. Falanga et al[102] reported that anti-ssDNA antibodies were frequent in generalized morphoea. Anti-ss-DNA antibodies were associated with joint contractures, deformities or more extensive, active and long-standing disease[102]. In another study, anti-histone antibodies were seen in 47% of cases having localized morphoea and 87% of those with generalized morphoea. The titres of anti-histone antibodies also give an idea about the number of plaques and the number of sites involved[75]. Anticardiolipin antibodies were also reported to be seen in cases with generalized type and linear type of morphoea.

IgM type of anticardiolipin antibodies was more commonly seen than IgG in generalised type[54]. Rheumatoid factor (RF) may be found in 39% of patients[6]. IgM type of antibodies are seen in almost 60% of cases and seems to correlate with severity of the disease[54,57]. Other antibodies like Scl-70, anti-centromere, Ro/La etc may indicate presence of systemic disease and such cases require regular check-ups for many years. It is still under speculation whether these auto-antibodies do really have a prognostic role[13]. Raised values of tumor necrosis factor alpha and IL-13 have been seen in morphoea patients as these promote fibrosis[57]. In a study conducted by Zulian et al[13] on 750 children, ANA was positive in 42%, rheumatoid factor in 16%, anticardiolipin antibody in 13%, anti ds DNA in 4%, Scl-70 in 3% and anticentromere antibody in 2%. Serum procollagen type 1 carboxy-terminal propeptide and type 3 procollagen propeptide have also shown raised values in patients with morphoea[104].

IMAGING

a) THERMOGRAPHY

The activity of a linear scleroderma lesion can be assessed by thermography[105]. This technique may detect temperature increase in active areas and areas of new lesions. A morphoea lesion is considered as thermographically active if its temperature differs by + 0.5Â°C from the adjacent area or from the contralateral limb[214]. Martini et al[105] compared the

thermographic assessment with the clinical description of lesions and showed that thermography had 92% sensitivity and 68% specificity.

b) ULTRASOUND

High frequency ultrasound shows details of the dermis and subcutaneous layers. The 20MHz ultrasound allows determining the depth and extent of sclerosis in the affected area and also monitoring the course of the disease[106]. In pediatric patients, it may show the loss of subcutaneous fat and muscle, increased blood flow and increased ecogenicity due to collagen condensation in the dermis. Hyperemia and the increasing ecogenicity seem to point to active lesions[107]. The major drawback of ultrasound is that it is an operator-dependent investigation so results may vary[107].

c) RADIOLOGICAL STUDIES

Radiological examination of skull and limbs may show underlying growth arrests. A peculiar condition called melorheostosis of bones howing cortical hyperostosis can be seen. Shortening of limbs, indurations of skull and other bony abnormalities like sacralization of lumbar vertebra, contracted pelvis, rib anomaly, atrophy of clavicle, spina bifida occulta, shortened ulna, kyphosis, and scoliosis and bone cysts can be made out[11].

d) MRI

MRI is not only used in cases with CNS involvement but also in deep and generalized morphoea to estimate the true depth of soft-tissue lesions. In the inflammatory phase, MRI may detect thickening of the dermis and infiltration of subcutaneous tissue, fascia and muscle as increased signal intensity on short tau inversion recovery (STIR) sequences and contrast enhanced T1-weighted images.

When bone is involved, a band like intense signal on T2-weighted and contrast-enhanced T1-weighted images are seen[108]. The main drawbacks of MRI are the need for sedation in younger cases and the presence of possible artifacts. MRI of the brain and skull in patients with en coup de sabre and Parry-Romberg syndrome may reveal abnormalities such as cortical atrophy, subcortical calcifications, white matter lesions, ventricular dilatation, leptomeningeal enhancement, anomalous intracranial vasculature and skull atrophy, even in the absence of neurological symptoms.

e) ELECTROENCEPHALOGRAM

Dysarrythmias in EEG underlying the lesional skin have been reported in frontoparietal morphoea.

f) OTHER TECHNIQUES

These include either laser Doppler flowmetry or laser Doppler imaging. A recent study of 41 children showed that morphoea plaques showed higher blood flow in comparision to normal areas[109].

CLINICAL ASSESSMENT

a) Localized Scleroderma Severity Index (LoSSI)

This index (LoSSI) is calculated on the basis of three parameters including extension of lesion, inflammation intensity and development of new lesions. 14 anatomic areas are examined and each area is divided into 3 segments. The score ranges from 0 to 168[110].

b) Computerized skin score (CSS)

This scoring requires the use of a computer software for comparing a single lesion over a span of time. It mainly separates hyperemic and indurated borders of plaques on a transparent film with different colours which is then transferred over a cardboard and scanned[111].

c) DUROMETER

It is a handheld instrument for measuring skin induration. The reading is based on factors including edema, site, sex and age of the patient. Seyger et al[112] found that although durometer findings showed less intra and interobserver variations but on comparing these measurements with clinical scores, a difference was noted.

d) CUTOMETER

A cutometer also requires a computer software and basically measures skin elasticity and relaxation. The results are influenced by location, age, sex, and edema. It is also a hand held device[113].

ROLE OF TGF-β 1 LEVELS

Recently, values of transforming growth factor β 1 (TGF β1) in a morphoea patient have been found to play a role as a disease activity marker but this requires further studies and is an area for future research. The values do not depend upon the type of clinical morphoea[114].

HISTOPATHOLOGICAL FINDINGS

There is not much difference in the biopsy findings of the various types of morphoea but they differ according to their depth of involvement. Ideally, a biopsy sample for morphoea should include tissue upto the level of subcutis as the pathology mainly involves the reticular dermis and the subcutis[115]. A deep punch biopsy is usually taken for circumscribed morphoea while an incisional biopsy is ideal for the other types[116]. Three main stages exist- Early inflammatory, intermediate, and late sclerotic.

The epidermis may be normal, atrophic or sometimes slightly thicker than usual[22].

EARLY STAGE

In the early inflammatory stage, found particularly at the violaceous border of enlarging lesions, the reticular dermis shows interstitial lymphoplasmacytic infiltrates among slightly thickened collagen bundles[115]. Vascular changes in the early inflammatory stage generally are mild both in the dermis and in the subcutaneous tissue. They may consist of endothelial swelling and edema of the walls of the vessels.

INTERMEDIATE STAGE

In the intermediate stage, the inflammatory infiltrates surround eccrine coils and are associated with hypocellular collagen bundles and reduced

numbers of surrounding adipocytes. A much more pronounced inflammatory infiltrate than that seen in the dermis often involves the subcutaneous fat and extends upward toward the eccrine glands. Trabeculae subdividing the subcutaneous fat are thickened because of the presence of an inflammatory infiltrate and deposition of new collagen. Large areas of subcutaneous fat are replaced by newly formed collagen, which is composed of fine, wavy fibers, rather than of bundles, and which stains only faintly with hematoxylin-eosin[117].

LATE SCLEROTIC STAGE

In late stage, as seen in the center of the old lesions, a square appearance is seen in the punch biopsy. The epidermis appears normal and the inflammatory infiltrate disappears completely except in few areas of subcutis. In the papillary dermis, the collagen bundles appear homogenous whereas in the reticular dermis they appear thickened, closely packed, and hypocellular, and stain more deeply eosinophilic than in normal skin. The eccrine glands appear markedly atrophic, appear surrounded by newly formed collagen and lie higher in the dermis as a result of the replacement of most of the subcutaneous fat by newly formed collagen. The collagen consists of thick, pale, sclerotic, homogeneous, or hyalinised bundles with only few fibroblasts thereby having a typical homogenous, hyalinised and hypocellular appearance[115]. There is paucity of blood vessels with narrowed

lumen and fibrotic walls and elastic stains show thick elastic fibers arranged in parallel to hypocellular collagen strands and in parallel to the epidermal surface.

BIOPSY FINDINGS IN DIFFERENT TYPES OF MORPHOEA

A) GUTTATE MORPHOEA

The changes are more superficial with less collagen sclerosis but with subepidermal edema.

B) LINEAR MORPHOEA

Linear lesions may show a deeper and more diffuse inflammatory cell infiltrate extending into the underlying muscle. Vascular changes are usually prominent. Ossification of the dermis has been recorded[118].

C) GENERALISED MORPHOEA

Initial stages show a lymphohistioplasmocytic inflammatory infiltrate in the subcutis. Late stages are characterized by hyalinised connective tissue which is responsible for the indurated skin[22].

D) CIRCUMSCRIBED MORPHOEA

1) SUPERFICIAL VARIANT

The collagen deposition and inflammation are restricted to the superficial dermis[119]. A mild lymphoplasmacytic infiltrate surrounds eccrine

ducts in the superficial dermis. Dermal elastic fibers are not appreciably diminished, but there is some loss of CD34-positive spindle cells[119].

2) DEEP VARIANT

There is thickening and hyalinisation of collagen in the deep dermis and in the septa and fascia. There is a mixed inflammatory cell infiltrate which includes some multinucleate giant cells. Lipomembranous (membranocystic) changes may be present. There may be marked fibrosis in the subcutis[120]. Vacuolation of the muscle fibres and interspersed edema thereby separating them along with focal inflammatory cells infiltrate are the other findings.

E) KELOIDAL MORPHOEA

There are hyalinised thick collagen bundles associated with an increase in fibroblasts and mucin[121].

F) BULLOUS MORPHOEA

Subepidermal edema with dilated lymphatics in the underlying dermis. Erythrocytes are often present in the blister[68].

DIRECT IMMUNOFLUORESCENCE

Immunofluorescence is usually negative in the lesions of localized scleroderma but it may show IgM deposition in the basement membrane and IgM and C3 deposition in blood vessels of dermis in one third of the cases of generalised morphoea and in few cases of linear morphoea[22].

ELECTRON MICROSCOPY

There is disarray and variable thickness of collagen at the advancing border[122]. Endothelial cells in blood vessels contain vacuoles and there is widening of the gap between the cells. Collagen fibrils in the subcutis have a reduced diameter.

HISTOCHEMISTRY

Subcutis shows only weak birefringence and trichrome staining and there is an increased number of fibroblasts. However, the collagen in the subcutis stains strongly with the PAS stain in contrast to the very weak staining of that in the dermis. Mucopolysaccharides are present in the early lesions, particularly in the subcutis. A study of glycosaminoglycans in normal and sclerodermatous skin has shown an increase in hyaluronic acid and altered dermatan sulphate in involved skin. Chemical analysis shows increased hexosamines and hexoses bound to collagen fibres. Sugars attached to the collagen give the homogenous appearance in eosin- haematoxylin stain. Immunohistochemistry studies have shown that morphoea mainly

shows foci of intercollagenous staining for connective tissue antigens in lower part of dermis[242], and that there is a reduction in the size and number of dermal papillae, with increased angiogenesis in the early inflamatory stage and various numbers of enlarged vessels in inactive lesions. A further study has reported an increase in dermal microvascular pericytes in the peripheral zones of active lesions, supporting the concept of a vascular pathogenesis of scleroderma[123].

Immunohistochemical characterization of the infiltrate has shown the presence of T lymphocytes of both CD4 and CD8 subtype, as well as Langerhans cells and natural killer cells[124].

PROGNOSIS

The expected natural history in morphoea is that of spontaneous resolution. Circumscribed morphoea usually resolves over 3 to 5 years[116]. Pigmentation is evident for many years in almost 33% of cases. Linear morphoea has a longer course as compared to circumscribed morphoea but severity decreases with time[22]. Morbid features are more commonly seen with linear and deep morphoea and include contractures, limb length abnormalities, calcinosis and atrophy of the face[116]. Torok and Ablonczy reported that most of lesions healed without any disability[125]. Morphoea cases have been rarely reported to progress to systemic sclerosis, prevalence

ranging from 1 to 6% according to one case report[126] and the presence of anti-Ku antibody may indicate such transformation[127]. Generalised morphoea patients show mild improvement over a span of 3 to 5 years, but there have been reports stating active disease 33 years after diagnosis[11] and another patient died of bronchiolitis obliterans organizing pneumonia[128].

TREATMENT

Usually the disease has a spontaneous resolution and it is not treated if there are no associated complications[22]. Treatment usually targets inflammatory activity in the early stages as once the disease progresses to the sclerosis stage, treatment is not of that much benefit[116].

Various topical measures like potent or superpotent topical steroids[129], 0.005% calcipotriene, 0.1 % tacrolimus[130] and 5% imiquimod [131] cream have been used. Intralesional steroids (triamcinolone acetonide, 5-10 mg/ml) have also been found to be helpful[129]. Topical photodynamic therapy has also been tried.

Systemic therapy used in morphoea includes phenytoin, *p*-aminobenzoate, griseofulvin, penicillin, etretinate, ciclosporin, vitamin D, vitamin E, chloroquine and hydroxychloroquine[22]. Regression of plaques of morphoea after tamoxifen therapy has also been reported[22]. Oral endothelin receptor antagonist bosentan was also found to be useful[22]. d-Penicillamine with or without pyridoxine is another modality which has been tried[22].

Methotrexate (15 mg/wk) has been used alone or with daily oral or pulsed high dose intravenous methyl prednisolone (1000 mg for 3 days monthly). Systemic corticosteroids (1- 2 mg/kg/day) have been found to be helpful[132], although they are effective only in the early inflammatory sages of morphoea.

Phototherapy might inhibit the sclerosing processes and play a role in skin softening. Several modalities like systemic and bath PUVA, UVA1, narrowband UVB therapy and extracorporeal photochemotherapy have also been tried[133].

Plasmapheresis (along with systemic steroids) has been reported to be helpful[134].

Physical therapy such as physiotherapy may be used to prevent deformities and contractures. In few cases, surgeries for contracture relief, limb lengthening and deformity correction have been found useful. Even plastic surgeons have played a role in cases with ECDS and those with ossification. Ulcers associated with bullous lesions have been treated with 'tissue engineered' skin.

AIM OF THE STUDY

1) To study the clinico-epidemiological features of morphoea and its various types.
2) To study the precipitating factors and other associated diseases.
3) To correlate the histopathological findings with the stage and various types of morphoea.

MATERIALS AND METHODS

This study was conducted in the Outpatient Department of Government Rajaji Hospital, Madurai during the period October 2010 to September 2012 (24 months).

INCLUSION CRITERIA

All consenting patients having

1) Lesions with clinical morphology consistent with morphoea.
2) Lesions which showed histopathological findings consistent with morphoea inspite of a diagnostic dilemma clinically.

EXCLUSION CRITERIA

1) Patients not willing to give consent for examination and biopsy.
2) Patients with lesions where diagnosis was a dilemma clinically and biopsy could not be performed due to various reasons.

All the patients attending the outpatient department of Dermatology, Government Rajaji Hospital were screened during the study period between October 2010 and September 2012 and patients satisfying the above mentioned criteria were enrolled in the study. After getting their informed consent, a detailed history was taken and a thorough dermatological and systemic examination was done.

The parameters studied were the age of onset, duration of lesions, sex, site, type of morphoea, side of involvement, symptoms, precipitating factors, evolution/ regression of lesions, past history, family history, birth history, number of lesions, sensation, contractures and associations. Histopatholgical examination was done for all the patients. Biopsy was taken from both the advancing edge as well as the centre for few cases and from any one site for rest. Relevant investigations like blood examination (complete haemogram, peripheral smear, renal function tests, blood sugar, liver function tests) and urine routine were done for all the cases. Investigations like ANA, radiological examination of chest, local part and spine were done for selected cases. Opinion of Neurologist and Ophthalmologist were obtained in patients of frontoparietal morphoea. All the data was further compiled and inferences were drawn.

OBSERVATIONS AND RESULTS

In this study, 54 cases of morphoea were encountered in the outpatient department of Dermatology, Government Rajaji hospital, Madurai during a study period of two years. The following observations were noted.

INCIDENCE

The total number of patients who attended the Skin O.P during the study period were 106368. The number of patients diagnosed with morphoea were 54 so the overall incidence of morphoea was found to be 0.5 per 1000 dermatology cases. (Table 1)

TABLE 1- INCIDENCE OF MORPHOEA

Total number of patients attending Skin O.P	106368
Patients diagnosed with morphoea	54
Incidence per 1000 cases	0.5

TYPES OF MORPHOEA

Out of the encountered 54 cases, circumscribed type of morphoea was the commonest with 28 (51.8%) cases followed by linear morphoea (including both limb and head variant) with 15 (27.8%) cases, generalised type with 5 (9.25%) cases, pansclerotic type with 3 (5.55%) cases and mixed type with 2 cases in the descending order. One case of keloidal morphoea was also seen. (Table 2, Figure1)

TABLE 2- TYPES OF MORPHOEA

TYPES OF MORPHOEA	NO. OF CASES	PERCENTAGE
CIRCUMSCRIBED TYPE	28	51.8%
LINEAR TYPE (HEAD VARIANT AND TRUNK/LIMB VARIANT)	15	27.8%
MIXED VARIANT TYPE	2	3.7%
GENERALISED TYPE	5	9.25%
PANSCLEROTIC TYPE	3	5.55%
OTHER TYPES (KELOIDAL)	1	1.8%
TOTAL	54	100%

Out of the 15 cases of linear morphoea, 27 % were classified under head variant and 73 % under trunk limb variant. (Table 3, Figure 2)

TABLE 3- TYPES OF LINEAR MORPHOEA

TYPES OF LINEAR MORPHOEA	NUMBER OF CASES
HEAD VARIANT a) En coup de sabre b) Progressive hemifacial atrophy	4 3 1
TRUNK LIMB VARIANT	11

SEX RATIO

In our study 14 cases (26%) were males and 40 cases (74%) were females, the overall female: male ratio being 2.85:1. (Table 4, Figure 3,4)

TABLE 4- SEX RATIO

CLINICAL TYPES	MALE	FEMALE	TOTAL
CIRCUMSCRIBED TYPE	6	22	28
LINEAR TYPE	5	10	15
MIXED TYPE	1	1	2
GENERALISED TYPE	0	5	5
PANSCLEROTIC TYPE	2	1	3
OTHERS	0	1	1
TOTAL	14	40	54

SIDE-WISE DISTRIBUTION

Overall, both sides were involved in maximum number of cases with 39% of the patients followed by right side involvement with 37% of the cases and left side involvement constituting 24%. The right side involvement dominated in the individual types with the exception of pansclerotic and generalised morphoea where both sides were more commonly involved. (Table 5, Figure 5,6)

TABLE 5- SIDE WISE DISTRIBUTION

CLINICAL TYPES	RIGHT	LEFT	BOTH
CIRCUMSCRIBED TYPE	11	9	8
LINEAR TYPE	7	3	5
MIXED TYPE	1	1	0
GENERALISED TYPE	0	0	5
PANSCLEROTIC TYPE	1	0	2
OTHERS	0	0	1
TOTAL	20	13	21

AGE OF ONSET

In our study, the minimum age at onset of the disease was 2 years and 3 months whereas the maximum age reported was 71 years. Age group 11-20 years was most commonly involved with 22 (40%) cases. (Table 6, Figure 7)

TABLE 6- AGE OF ONSET- OVERALL

AGE IN YEARS	MALES	FEMALES	TOTAL	PERCENTAGE
0 – 5	0	4	4	7.5%
6- 10	3	7	10	18.5%
11- 20	8	14	22	40%
21- 30	1	6	7	13.25%
31- 40	1	3	4	7.5%
41- 50	0	5	5	9.25%
> 50	1	1	2	4%

AGE OF ONSET WISE DISTRIBUTION OF CIRCUMSCRIBED TYPE

The commonest age group involved was 11-20 years with 11(39.5%) cases.

(Table 7, Figure 8)

TABLE 7- AGE OF ONSET (CIRCUMSCRIBED TYPE)

AGE IN YEARS	MALES	FEMALES	TOTAL
0 -5	0	4	4
6- 10	1	5	6
11- 20	3	8	11
21- 30	1	1	2
31- 40	0	1	1
41- 50	0	2	2
> 50	1	1	2

AGE OF ONSET WISE DISTRIBUTION OF LINEAR TYPE

The commonest age group involved was 11-20 years with 5 (33.3%) cases. (Table 8, Figure 9)

TABLE 8- AGE OF ONSET (LINEAR TYPE)

AGE IN YEARS	MALES	FEMALES	TOTAL
0-5	0	0	0
6- 10	1	1	2
11- 20	3	2	5
21- 30	0	4	4
31- 40	1	2	3
41- 50	0	1	1
> 50	0	0	0

AGE OF ONSET WISE DISTRIBUTION OF GENERALISED TYPE

The commonest age group involved was 41-50 years with 2 (40%) cases. (Table 9, Figure 10)

TABLE 9- AGE OF ONSET (GENERALISED TYPE)

AGE IN YEARS	MALES	FEMALES	TOTAL
0 – 5	0	0	0
6- 10	0	1	1
11- 20	0	1	1
21- 30	0	1	1
31- 40	0	0	0
41- 50	0	2	2
> 50	0	0	0

AGE OF ONSET WISE DISTRIBUTION OF PANSCLEROTIC TYPE

All the cases occurred in the age group 11-20 years. (Table 10, Figure 11)

TABLE 10- AGE OF ONSET (PANSCLEROTIC TYPE)

AGE IN YEARS	MALES	FEMALES	TOTAL
0 – 5	0	0	0
6- 10	0	0	0
11- 20	2	1	3
21- 30	0	0	0
31- 40	0	0	0
41- 50	0	0	0
> 50	0	0	0

AGE OF ONSET WISE DISTRIBUTION OF OTHER TYPES

Only one case of keloidal morphoea was seen in the age group 11-20 years.

AGE OF ONSET WISE DISTRIBUTION OF MIXED TYPE

One case was seen in 6-10 years age group and other in 11-20 years age group

DURATION OF LESIONS

The duration of lesions at the time of presentation was in the range of 6 months - 2 years most commonly with 22 (41%) cases. (Table 11, Figure 12)

TABLE 11- DURATION OF LESIONS

DURATION OF LESIONS	MALE	FEMALE	TOTAL	PERCENTAGE
0-6 mo	7	14	21	39%
6mo- 2 years	3	19	22	41%
2-5 years	2	3	5	9%
>5 years	2	4	6	11%

SITE WISE DISTRIBUTION- TOTAL

Overall, multiple sites involvement was seen in 25 cases (46%) and 29 cases (54%) showed single site involvement.

SINGLE SITE INVOLVEMENT- 29 CASES

In cases where only one site was involved, back and lower limbs were the most commonly involved sites with 28% cases each. (Table 12, Figure 13)

TABLE 12- SITE WISE DISTRIBUTION-SINGLE SITE

SITE	NUMBER OF PATIENTS	PERCENTAGE
HEAD AND NECK a) FOREHEAD AND SCALP b) FACE c) BOTH	6 3 2 1 0	20%
CHEST	0	-
BACK	8	28%
ABDOMEN	1	4%
UPPER LIMBS	6	20%
LOWER LIMBS	8	28%

MULTIPLE SITES INVOLVEMENT- 25 CASES

In multiple sites involvement, upper limbs were most commonly involved with 72% of cases. (Table 13, Figure14)

TABLE 13- SITE WISE DISTRIBUTION- MULTIPLE SITES

SITE	NUMBER OF PATIENTS	PERCENTAGE
HEAD AND NECK a) FOREHEAD AND SCALP b) FACE	5 2 3 0	20%
CHEST	6	24%
BACK	10	40%
ABDOMEN	11	44%
UPPER LIMBS	18	72%
LOWER LIMBS	13	52%

SITE WISE INVOLVEMENT OF CIRCUMSCRIBED TYPE

Circumscribed morphoea affected back most commonly in our study with 8 cases (28.5%). (Table 14, Figure 15)

TABLE 14- SITE WISE INVOLVEMENT (CIRCUMSCRIBED TYPE)

SITE	NUMBER OF PATIENTS	PERCENTAGE
HEAD AND NECK a) FOREHEAD AND SCALP b) FACE	2 1 1	7%
CHEST	0	-
BACK	8	28.5%
ABDOMEN	1	3.5%
UPPER LIMBS	4	14.5%
LOWER LIMBS	5	18%
MULTIPLE SITE INVOLVEMENT	8	28.5%

SITE WISE INVOLVEMENT OF LINEAR TYPE

Multiple site involvement was most common in linear type with 8 cases (53%). Within multiple sites involvement, upper limbs were more commonly involved with 7 cases as compared to 3 cases where lower limbs were involved. (Table 15, Figure 16)

TABLE 15- SITE WISE INVOLVEMENT (LINEAR TYPE)

SITE	NUMBER OF PATIENTS	PERCENTAGE
HEAD AND NECK a) FOREHEAD AND SCALP b) FACE c) BOTH	4 2 1 1	27%
UPPER LIMBS	1	7%
LOWER LIMBS	2	13%
MULTIPLE SITE INVOLVEMENT	8	53%

SITE WISE DISTRIBUTION OF MIXED TYPE

Multiple sites were involved in both the cases.

SITE WISE DISTRIBUTION OF PANSCLEROTIC TYPE

Two cases involved lower limbs as well as upper limbs, out of which one involved all the 4 limbs. One female case showed involvement of just right lower limb.

SITE WISE DISTRIBUTION OF GENERALISED TYPE

Multiple sites were involved in all the 5 cases.

SITE WISE DISTRIBUTION OF OTHER (KELOIDAL) TYPE

Right side of chest and left side of abdomen showed keloidal lesion over the morphoea plaques.

SYMPTOMS

Although morphoea was mostly asymptomatic (42.6% of cases) but the commonest complaint reported was itching in 19 cases (35.2%). (Table 16, Figure 17)

TABLE 16- SYMPTOMS

COMPLAINTS	NO. OF PATIENTS	PERCENTAGE
Nil	23	42.6%
Itching	19	35.2%
Discolouration	9	17%
Disfigurement	4	7.5%
Arthralgia	4	7.5%
Headache	3	5.5%
Raynauds phenomenon	1	1.9%

EVOLUTION OF LESIONS

43 cases were in the progressing stage, 10 cases showed static lesions and 1 case was reported in the regressing stage. (Table 17, Figure 18)

TABLE 17- EVOLUTION OF LESIONS

EVOLUTION OF LESIONS	NO. OF PATIENTS	PERCENTAGE
PROGRESSING	43	79.5%
STATIC	10	18.5%
REGRESSING	1	2%

PRECIPITATING FACTORS

Most of the cases in this study did not have any precipitating factors but 4 cases gave history of trauma at the site of morphoea whereas 1 patient developed the disease while she was pregnant. (Table 18, Figure 19)

TABLE 18- PRECIPITATING FACTORS

PRECIPITATING FACTORS	NO. OF PATIENTS	PERCENTAGE
Nil	49	90.7%
Pregnancy	1	1.9%
Trauma	4	7.4%

PAST AND FAMILY HISTORY

There was no patient who gave a past history of morphoea and just one patient had similar illness in the family with mother having circumscribed type of morphoea.

BIRTH HISTORY

In our study, 46 cases (85%) were born out of non consanguineous marriage followed by 3rd degree consanguineous marriage with 5 cases (9.5%). (Table 19, Figure 20)

TABLE 19- BIRTH HISTORY

CONSANGUINITY	NUMBER OF PATIENTS	PERCENTAGE
NON CONSANGUINEOUS	46	85%
2ND DEGREE CONSANGUINEOUS	3	5.5%
3RD DEGREE CONSANGUINEOUS	5	9.5%

ASSOCIATED SYSTEMIC DISEASES

Almost 90% did not have any associated systemic diseases but Diabetes mellitus and Hypertension were seen in 3.7% of cases each. (Table 20, Figure 21)

TABLE 20- ASSOCIATED SYSTEMIC DISEASES

ASSOCIATED SYSTEMIC DISEASES	NUMBER OF PATIENTS	PERCENTAGE
BRONCHIAL ASTHMA	1	1.9%
DIABETES MELLITUS	2	3.7%
HYPERTENSION	2	3.7%
NIL	49	90.7%

NUMBER OF LESIONS

Most of the cases in our study had multiple lesions, 67% to be exact. (Table 21, Figure 22)

TABLE 21- NUMBER OF LESIONS

NUMBER OF LESIONS	NUMBER OF PATIENTS	PERCENTAGE
SINGLE	18	33.4%
MULTIPLE	36	66.6%

SENSATION

Out of the 54 patients, 3 patients had variable loss of sensation over the lesions. (Table 22)

TABLE 22- SENSATION

SENSATION	NO. OF PATIENTS
INTACT	51
VARIABLE LOSS	3
PERCENTAGE	5.55%

CONTRACTURES

Out of the 54 patients, all 3 patients with pansclerotic morphoea had contractures. (Table 23)

TABLE 23- CONTRACTURES

TOTAL NUMBER OF PATIENTS	54
PATIENTS WITH CONTRACTURES	3
PERCENTAGE	5.55%

HEMIATROPHY

No. of patients showing hemiatrophy of tongue- 2.

No. of patients showing hemiatrophy of face- 1. (Table 24, Figure 23)

TABLE 24- HEMIATROPHY

TOTAL NUMBER OF PATIENTS	54
PATIENTS WITH HEMIATROPHY	3
PERCENTAGE	5.55%

COMPLETE BLOOD COUNT

10 patients (18.5%) out of 54 showed eosinophilia and 6 patients (11%) had anaemia. (Table 25, Figure 24)

TABLE 25- COMPLETE BLOOD COUNT

ABNORMALITY	NO. OF PATIENTS	PERCENTAGE
NIL	42	77.8%
ANAEMIA	6	11%
EOSINOPHILIA	10	18.5%

LIVER FUNCTION TESTS

Only one patient with circumscribed morphoea showed abnormal liver function tests with raised liver enzymes.

HISTOPATHOLOGY

SITE OF BIOPSY

Biopsy was taken from the centre of the lesion for most of the cases (68.5%). (Table 26, Figure 25)

TABLE 26- SITE OF BIOPSY

SITE OF BIOPSY	NUMBER OF PATIENTS	PERCENTAGE
EDGE	7	13%
CENTRE	37	68.5%
BOTH	10	18.5%

Out of the 44 cases from which biopsy was taken from a single site, 54.5% of cases were classified as early morphoea and intermediate and late stages accounted for 29.5% and 13.5% respectively. 2.5% of cases had features of more than one stage. (Table 27, Figure 26)

TABLE 27-HISTOPATHOLOGICAL STAGE OF MORPHOEA

STAGE OF MORPHOEA	NUMBER OF PATIENTS	PERCENTAGE
EARLY STAGE	24	54.5%
INTERMEDIATE STAGE	13	29.5%
LATE STAGE	6	13.5%
OVERLAP OF TWO STAGES	1	2.5%

NAIL CHANGES

Leukonychia and nail dystrophy were most commonly seen in 3.7 % cases. (Table 28, Figure 27)

TABLE 28- ASSOCIATED NAIL CHANGES

NAIL CHANGES	NO. OF PATIENTS	PERCENTAGE
NIL	49	90.7%
LEUKONYCHIA	2	3.7%
MELANONYCHIA	1	1.9%
NAIL DYSTROPHY	2	3.7%

ASSOCIATED SKIN DISEASES

The commonest skin disease which was found to be associated was LSA in 7.4 % cases. (Table 29, Figure 28)

TABLE 29- ASSOCIATED SKIN DISEASES

DISEASES	NO. OF PATIENTS
NIL	43
HYPERTROPHIC SCAR	1
KELOID	1
PSORIASIS	1
LICHEN SCLEROSUS ET ATROPHICUS	4
SEBORRHEIC MELANOSIS	1
LICHEN STRIATUS	1
VITILIGO	2
COLLOID MILIUM	1
BECKER'S NEVUS	1

DISCUSSION

We encountered 54 cases of morphoea in this study which was done for a span of 2 years.

INCIDENCE

Out of a total 106368 cases visiting the dermatology outpatient department during the study period, the cases with morphoea were 54 in total. Thus the incidence rate of morphoea was 0.5 per 1000 dermatology cases. In a study done by Peterson et al[12] in Olmsted county between 1960-1993 on 82 cases showed the incidence rate as 0.027 per 1000 population.

INCIDENCE OF VARIOUS CLINICAL TYPES

The incidence of various clinical types of morphoea in our study was as follows

Circumscribed- 51.8%

Linear (Head and trunk/limb variant)- 27.8%

Generalised- 9.25%

Pansclerotic- 5.55%

Mixed- 3.7%

Other unclassified variants (Keloidal morphoea) - 1.8%

Out of the 15 cases of linear morphoea, 27 % were classified under head variant and 73 % under trunk limb variant.

Our findings were in concurrence with the study conducted by Peterson et al[12] on 82 cases which reported that 56% of patients had plaque type morphoea, 20% linear, 13% generalized and 11% had deep morphoea. A study by Christianson et al[11] of 235 cases showed an incidence of 35% of plaque type, and 46% of linear type and 19% of generalized morphoea.

SEX RATIO

The overall sex distribution in our study pointed towards a female predominance with female to male ratio being 2.85:1. This was found to be consistent with studies conducted by Christianson et al[11] and Peterson et al[12] with ratios being 3:1 and 2.6:1 respectively. The individual types of morphoea also followed a similar pattern with exception of pansclerotic morphoea where males were reported to be more commonly involved. Linear morphoea in our study showed a female to male ratio as 2:1 whereas Peterson et al[12] reported an even sex distribution.

SIDE DISTRIBUTION

Bilateral involvement was seen in 39% of cases whereas 61% cases showed unilateral involvement with right side being involved in 37% of cases and left side in 24% of cases. Circumscribed morphoea showed unilateral

involvement more commonly with ratio being 2.5:1 as compared to cases with bilateral involvement.

Of the linear morphoea cases, head variant was seen more commonly on left side but one case of bilateral en coup de sabre was also seen. A similar case has been reported in the literature before by Dilley et al[72]. The trunk limb variant showed unilateral involvement more commonly with ratio being 2:1 in comparision to bilateral involvement. Right side was more commonly involved. One patient showed involvement of all the four limbs.

Christianson et al[11] also reported unilateral involvement more commonly in linear morphoea with 102 cases as compared to 6 cases with bilateral involvement. On the other hand, plaque morphoea was reported more commonly showing bilateral involvement with ratio being 3:1 in contradiction to our study.

Christen-Zaech et al[20] in his study on paediatric morphoea on 136 patients reported that 74% of patients with plaque type showed unilateral involvement which was 71% in our study.

Previous reports state that bilateral involvement in linear morphoea of children ranges from 5 to 25%[13,20] which was 33 % in our study.

AGE OF ONSET

The youngest child reported to have morphoea in our study was of age 2 years and 3 months and the maximum age reported was 71 years.

Christianson et al[11] reported the extremes of age as 1 year and 76 years. In this study, the maximum number of patients were seen in the age group 11 to 20 years with 40% of cases belonging to this age group whereas in the study conducted by Christianson et al[11], the peak incidence was between 20 to 40 years with 40 % of cases. The circumscribed type was also seen most commonly in the age group 11 to 20 years. In our study, incidence of plaque type below 10 years was 40% and between 20 to 50 years was 18%. In Christianson's study[11], incidence of the same below 10 years was 10% and between 20 to 50 years was 75 %.

The commonest age group involved in linear morphoea was 11-20 years with 33.3% cases. In our study, incidence of linear type below 10 years was 13% and below 40 years was 93%. Christianson's study[11] showed 10% incidence below 10 years and 75% below 40 years. So this finding supports that linear morphoea is more commonly seen in children than adults.

Peterson et al[12] reported in his study that 67% of patients were diagnosed before 18 years. In our study, this number was 47 %. Generalised morphoea was most commonly seen in the age group 41-50 years with 40%

cases. In our study, onset occurred in 80% of cases within age group 11 to 50 years which was in concurrence with the study conducted by Christianson et al[11] which also showed the same 80 %. All three cases of pansclerotic morphoea occurred in the age group 11-20 years and there was a case of keloidal morphoea which also occurred in the same age group. Out of 3 pansclerotic cases, 2 had their age of onset before 14 years in our study. This was also noted by Holmes et al[82].

Both cases of mixed morphoea had their age of onset between 6 to 20 years of age.

DURATION OF LESION

The maximum number of cases presented with lesions present for 6 months to 2 years with 41 % cases. 80% of the cases had the lesions for less than 2 years.

SITE OF DISTRIBUTION

Overall, single site involvement was seen in 54% of the cases with back and lower limbs being the commonest sites involved with 28% of the cases each and were closely followed by head/neck and upper limbs with 20% cases each. In multiple sites involvement, upper limbs were most commonly involved with 72% of cases.

Circumscribed morphoea affected back most commonly in our study with 28.5% cases. Multiple site involvement was most common in linear type with 53% cases. Within multiple sites involvement, upper limbs were more commonly involved.

SYMPTOMS

Most of the cases in our study were asymptomatic with 42.6% cases but itching was the most common complaint noticed with 35.2% of cases. Christianson et al[11] in his study on 235 cases reported arthralgia as the commonest symptom with 44% of cases whereas in our study only 7.5% of the cases had arthralgia.

One patient also reported with Raynaud's phenomenon (2%).

EVOLUTION OF LESIONS

In this study 79.5% of the patients had lesions which were still progressing at the time of presentation, 18.5 % had static lesions and one patient reported with regressing lesions. No other study could be found for comparision.

PRECIPITATING FACTORS

90 % of the cases in our study did not have any precipitating factors but trauma preceded the lesions in 7.4% of the cases. One female patient

(2%) developed morphoea lesions during pregnancy which was diagnosed as linear morphoea later.

Christianson et al[11] also reported similar findings with trauma being he commonest precipitating factor with 7.4% cases involved. Infections also accounted for 7% of cases. Pregnancy was seen as a precipitating factor in 3% of cases in this study.

GENETIC INFLUENCE

One female patient diagnosed as generalised morphoea gave family history of morphoea lesions in her mother. Also 15% of the patients in our study were born out of consanguineous marriage thereby giving support to the studies conducted by DeKeyser F et al[38], Kuhnl P et al[39] on the role of genetic factors in aetiology of the disease.

ASSOCIATED SYSTEMIC DISEASES

Almost 90% did not have any associated systemic diseases but diabetes mellitus and hypertension were seen in 3.7% of cases each. One case had bronchial asthma as well. Leitenberger JJ et al[52] on his study on 245 adult and pediatric cases reported 2% of cases with diabetes.

NUMBER OF LESIONS

Most of the cases in our study had multiple lesions, 67% to be exact.

CONTRACTURES AND HEMIATROPHY

All 3 patients with pansclerotic morphoea reported with contractures. One female patient, diagnosed as Parry Romberg syndrome had hemiatrophy of face and two male patients with pansclerotic morphoea were found to have hemiatrophy of tongue. One female and one male patient with pansclerotic morphoea also had atrophy of right lower extremity.

Christianson et al[11] reported that atrophy or contracture or both of one or more extremities were noted in 11% of the patients which was 6% in our study.

BLOOD INVESTIGATIONS

18.5% of patients in our study showed eosinophilia. On reviewing the literature, eosinophilia has been reported in 7 to 50% of cases with Marzano et al[16] reporting it in 7% , Christen-Zaech et al[20] and Zulian et al[13] reporting in 18% and Falanga et al[102] found 50% association. So, our findings were consistent with Christen-Zaech et al[20] and Zulian et al[13].

Anaemia was also seen in 11% of patients in our study.

HISTOPATHOLOGY

Biopsy was done for all cases included in the study and the cases were classified into early, intermediate and late morphoea according to the histopathological findings. Biopsy was taken from the centre of lesion in 68.5% cases, both the advancing edge as well as the centre for 18.5% cases

and just from the edge in 13% cases. Out of the 44 cases in which biopsy was taken from a single site either centre or edge, 54.5% of cases were classified as early morphoea and intermediate and late stages accounted for 29.5% and 13.5% respectively. 2.5% of cases had features of more than one stage. Out of the 10 cases in which biopsy was done from both edge as well as centre, 9 cases showed features of early morphoea from the edge whereas centre showed features of either intermediate or late morphoea.

All cases in which biopsy was taken from just the edge (7 cases) showed features of early morphoea.

Out of the 37 cases in which biopsy was done from centre, 46% (17) of cases showed features of early morphoea, 35% (13) showed features of intermediate morphoea, 16% (6) late morphoea and 3% (1) had overlap of more than one stage.

On reviewing the duration of lesions for these cases, we observed that 16 out of 17 cases (94.1%) classified as early morphoea histopathologically had lesions for a duration ranging between 1 to 6 months.

Similarly, 11 out of 13 cases (85%) classified as intermediate morphoea histopathologically had lesions for a duration ranging between 6 months to 2years.

All 6 cases (100%) classified as late morphoea histopathologically had lesions for more than 2 years.

Although no previous studies were found in the literature with similar findings but there was a definite correlation between the duration of lesions and histopathological findings in our study.

In a female case of circumscribed morphoea, a sub epidermal space was seen on histopathological examination.

In almost all the cases of linear morphoea, an interesting observation was made with more extensive inflammatory cell infiltrate extending till subcutaneous tissue.

A case of nodular/keloidal morphoea showed classical histopathological findings of keloid and early stage of morphoea. The keloidal lesion showed whorled, nodular mass of collagen interspersed with fibroblasts and the morphoea lesion showed homogenous, hyalinised, hypocellular collagen and high uptake of eccrine glands.

Biopsy was done for two cases of morphoea from associated lesions which clinically resembled Lichen sclerosus et atrophicus and they showed the classical histopathological features of LSA.

Another case had associated lichenoid lesion and biopsy showed the findings of lichen striatus.

One female with pansclerotic morphoea developed psoriasis like lesion over the morphoea plaque which was biopsied and showed features consistent with psoriasis.

Epidermis was either normal or atrophic in all the cases. Pigmentation of epidermis was observed in 5 cases.

ASSOCIATED SKIN DISEASES

The commonest skin disease which was found to be associated with morphoea in our study was LSA in 7.4 % cases. Other diseases were vitiligo, hypertrophic scar, keloid, lichen striatus, psoriasis, seborrheic melanosis, colloid milium, becker's nevus. There have been reports of association with becker's nevus[96], psoriasis[26], LSA[11] and vitiligo[93] in the literature.

SUMMARY

1. Total number of cases encountered were 54.
2. Incidence of morphoea was 0.5 in 1000 dermatology cases.
3. The incidence of various clinical types of morphoea was circumscribed- 51.8% , linear (head and trunk/limb variant)- 27.8%, generalised- 9.25%, pansclerotic- 5.55%, mixed- 3.7%, other unclassified variants (Keloidal morphoea) -1.8%
4. The female to male sex ratio was 2.85:1.
5. Right side was more commonly involved than left.
6. Circumscribed as well as linear morphoea showed unilateral involvement more commonly.
7. A case of bilateral en coup de sabre was reported.
8. A case of linear morphoea with involvement of all the four limbs was reported.
9. The maximum number of cases was reported in the age group 11 to 20 years.
10. Individual types were also seen most commonly in age group 11 to 20 years except generalised morphoea.
11. 54% cases showed single site involvement with back and lower limbs being most commonly involved.

12. Circumscribed morphoea affected back most commonly with 28.5% cases.
13. Multiple site involvement was most common in linear type with 53% cases.
14. Most cases were asymptomatic but when symptomatic, itching was the commonest complaint seen in 35.2% cases.
15. 79.5% of the patients had lesions which were progressing.
16. Trauma was seen as a precipitating factor in 7.4% cases and pregnancy in a single case.
17. Family history of morphoea was present in one case.
18. Diabetes mellitus, Hypertension and Bronchial asthma were the systemic associations reported.
19. Most of the cases had multiple lesions, 67% to be exact.
20. All patients with pansclerotic morphoea had contractures.
21. Hemiatrophy of face was seen in one patient and hemiatrophy of tongue in two cases.
22. Two patients had atrophy of right lower extremity.
23. Eosinophilia was seen in 18.5% of patients.
24. Features of early morphoea were seen in all the cases in which biopsy was taken from the edge.
25. A definite correlation between the duration of lesions and histopathological stage of morphoea was also observed.

26. A subepidermal space was also seen in the biopsy of one patient.
27. Another interesting observation was that all cases of linear morphoea showed a more extensive and deep infiltrate.
28. A rare case of nodular/keloidal morphoea showed foci of increased fibrosis amidst acellular, hyalinised collagen.
29. A colocalization of psoriatic lesions over morphoea plaque was seen which was confirmed histopathologically.
30. Other associated skin conditions reported were LSA, vitiligo, hypertrophic scar, keloid, psoriasis, lichen striatus, seborrheic melanosis, colloid milium, becker's nevus.

CONCLUSION

The incidence of morphoea was 0.5 per 1000 dermatology cases, the most common type being circumscribed followed by linear, generalised, pansclerotic and mixed in the descending order. The disease was more common in females with more number of lesions occurring on right side as compared to left. The maximum number of cases occurred in younger age group with second decade being the commonest. This age distribution held good even for individual subtypes of morphoea with the exception of generalised type which was seen in the middle aged. Back and lower limbs were the commonest sites involved overall. Most of the cases presented without any complaints but when symptomatic, itching was the commonest complaint. There were no triggering factors in most of the cases but few patients gave history of trauma prior to the onset of the lesions. A rare case of bilateral en coup de sabre was also reported and a case of linear morphoea showed involvement of all the four limbs. Contractures were seen in patients with pansclerotic morphoea. Rare findings like hemiatrophy of face and tongue were also reported. Atrophy of right lower extremity was also seen in two cases. Eosinophilia was the commonest blood abnormality seen.

Histopathological examination also showed various interesting observations in this study. As reported by authors before, the biopsies taken from the edge

of the lesion showed the features of early morphoea. Another interesting observation was that a definite correlation was seen between the duration of lesions and histopathological stage of morphoea though no similar studies were found in the literature for comparision and validation of this finding. Also, specimens taken from linear morphoea patients showed a more extensive and deep inflammatory infiltrate. A rare case of nodular/keloidal morphoea showed foci of increased fibrosis amidst acellular, hyalinised collagen. Another rare presentation of colocalization of psoriatic lesions over morphoea plaque was seen in one case which was confirmed histopathologically. Various cutaneous and extracutaneous associations were also found in this study.

FIGURE 1- TYPES OF MORPHOEA-PERCENTAGE

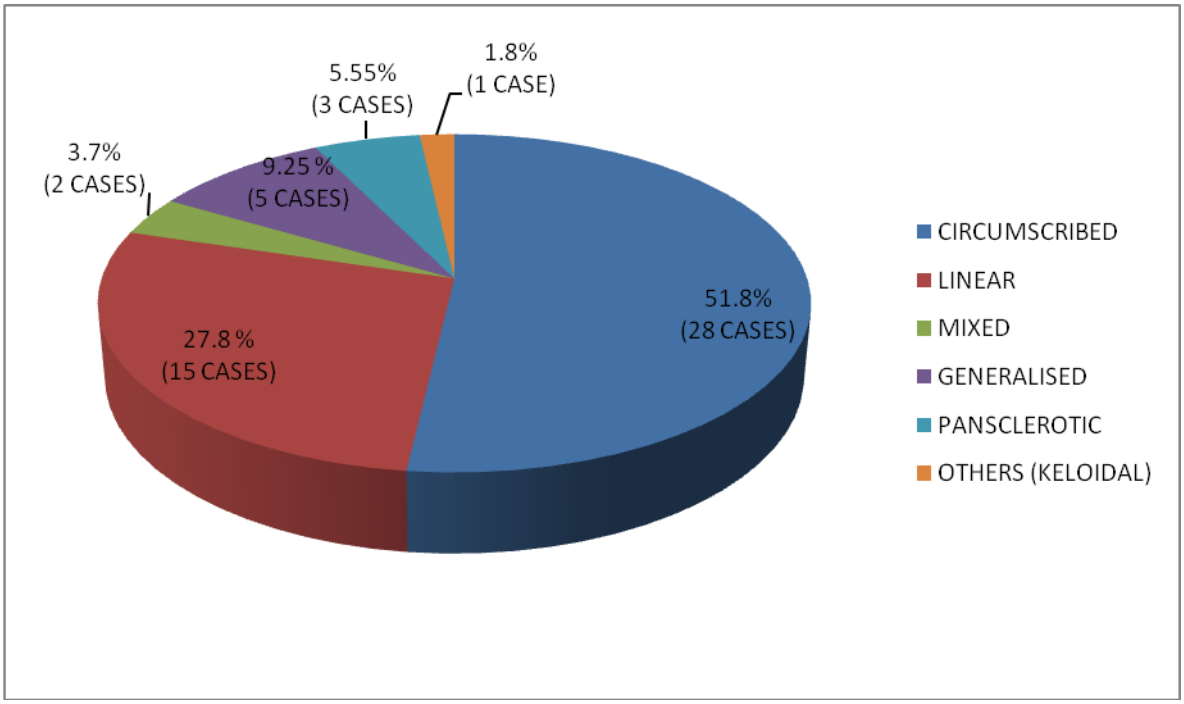


FIGURE 2- TYPES OF LINEAR MORPHOEA

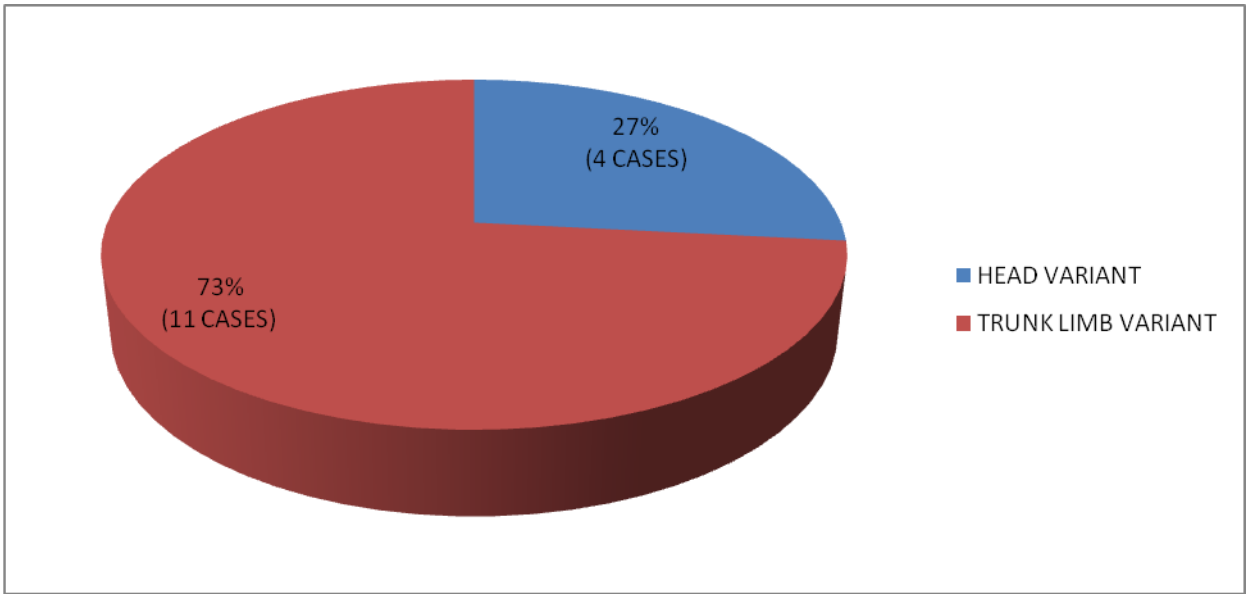


FIGURE 3- SEX RATIO

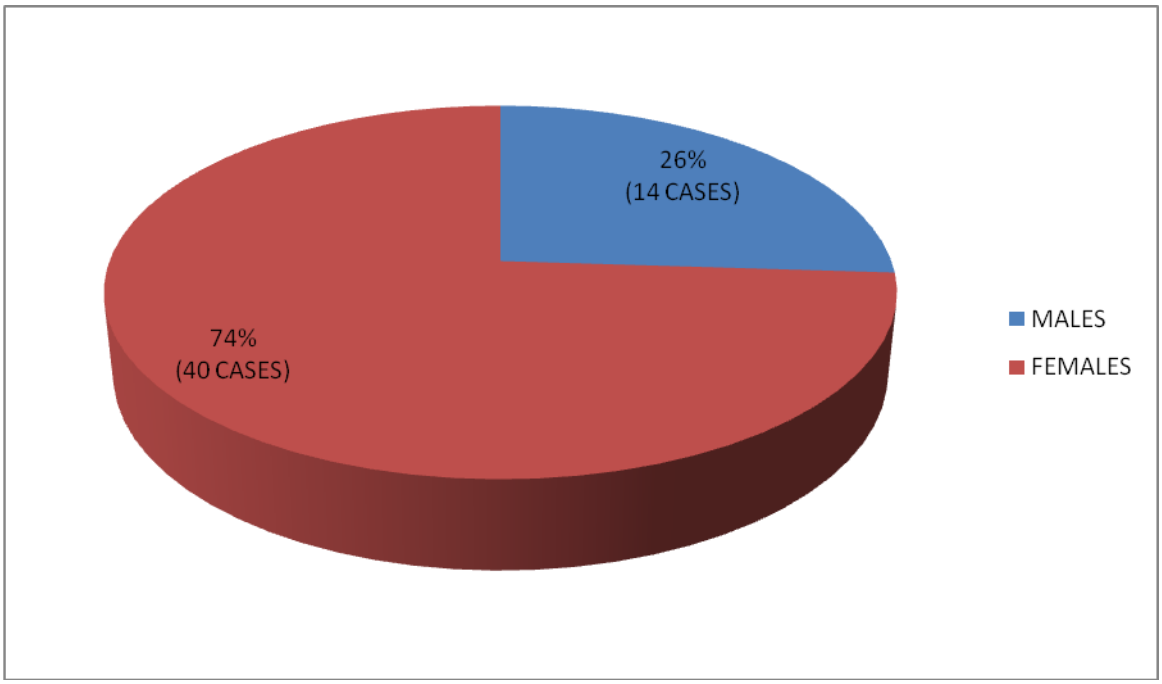


FIGURE 4- SEX WISE DISTRIBUTION OF DIFFERENT TYPES

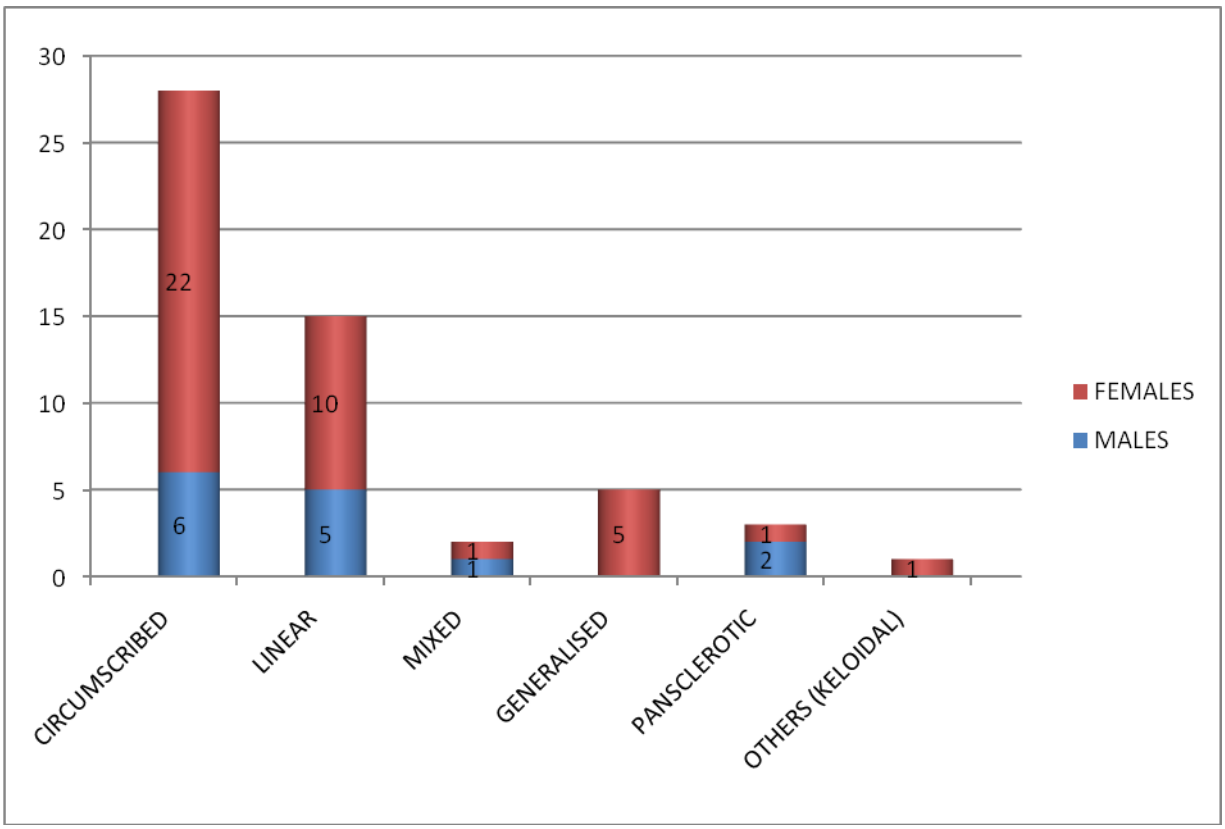


FIGURE 5- SIDE WISE DISTRIBUTION- TOTAL

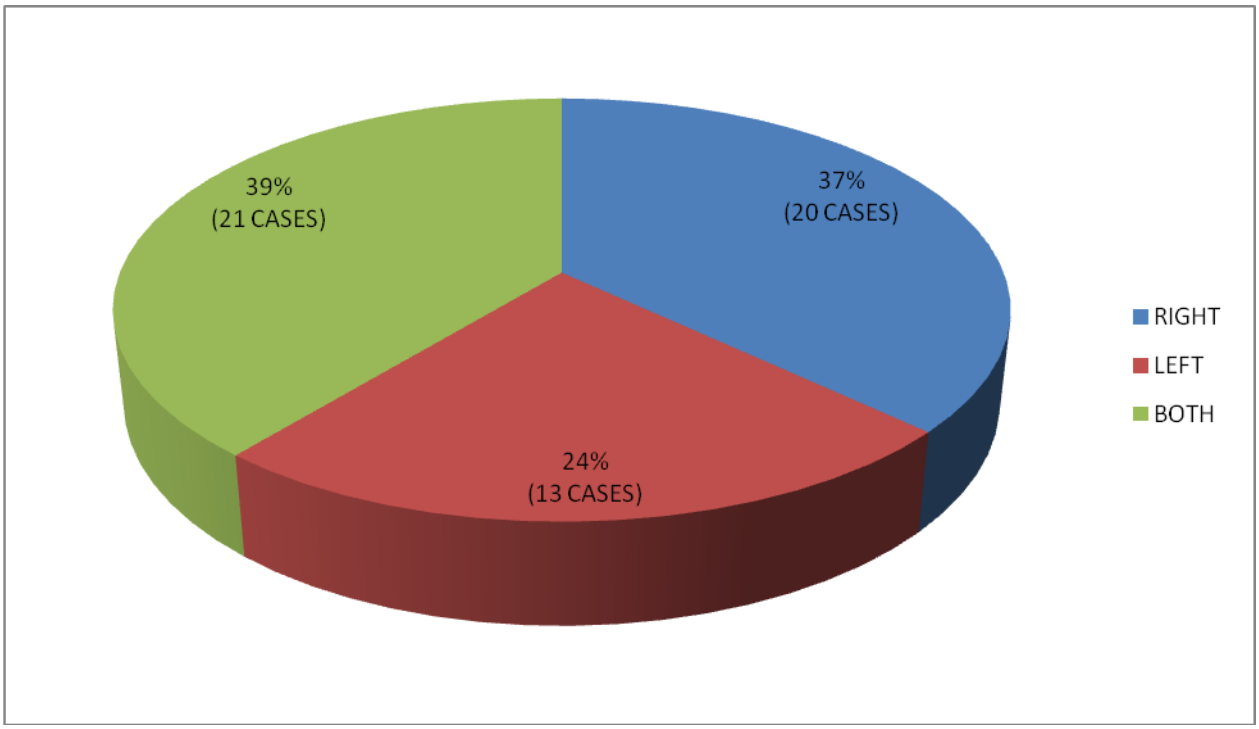


FIGURE 6- SIDE WISE DISTRIBUTION IN DIFFERENT TYPES OF MORPHOEA

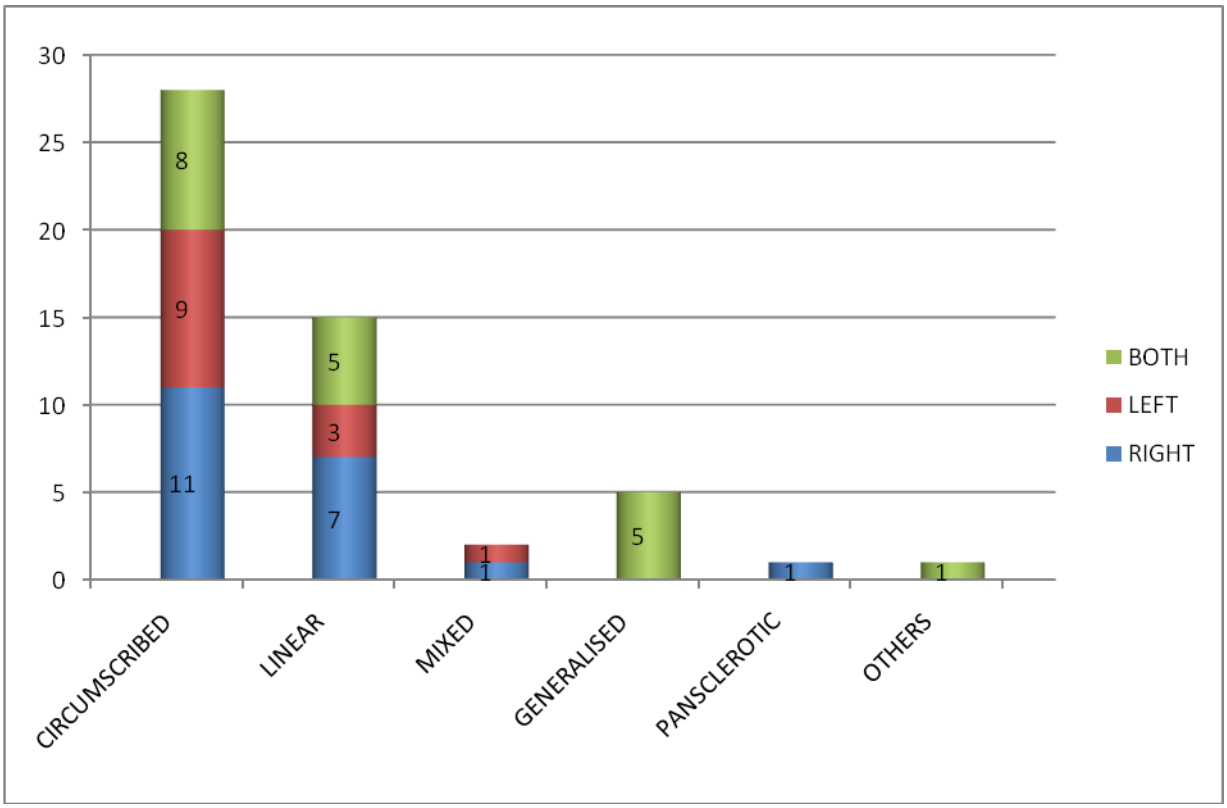


FIGURE 7- AGE OF ONSET -OVERALL

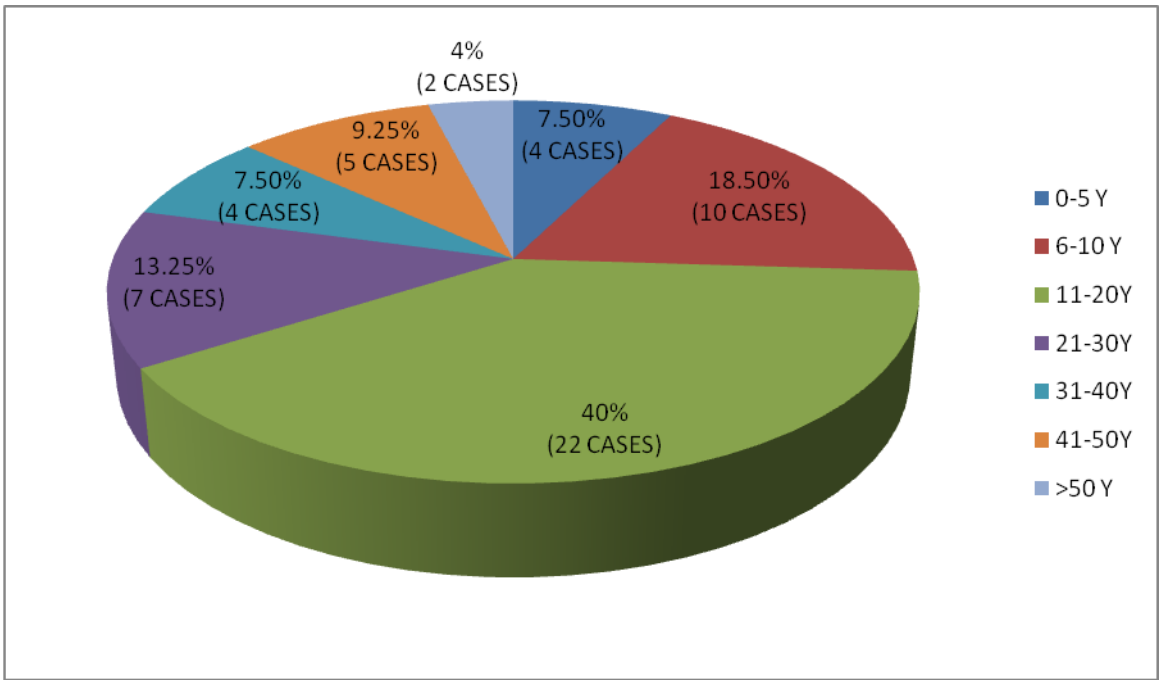


FIGURE 8- AGE OF ONSET (CIRCUMSCRIBED TYPE)

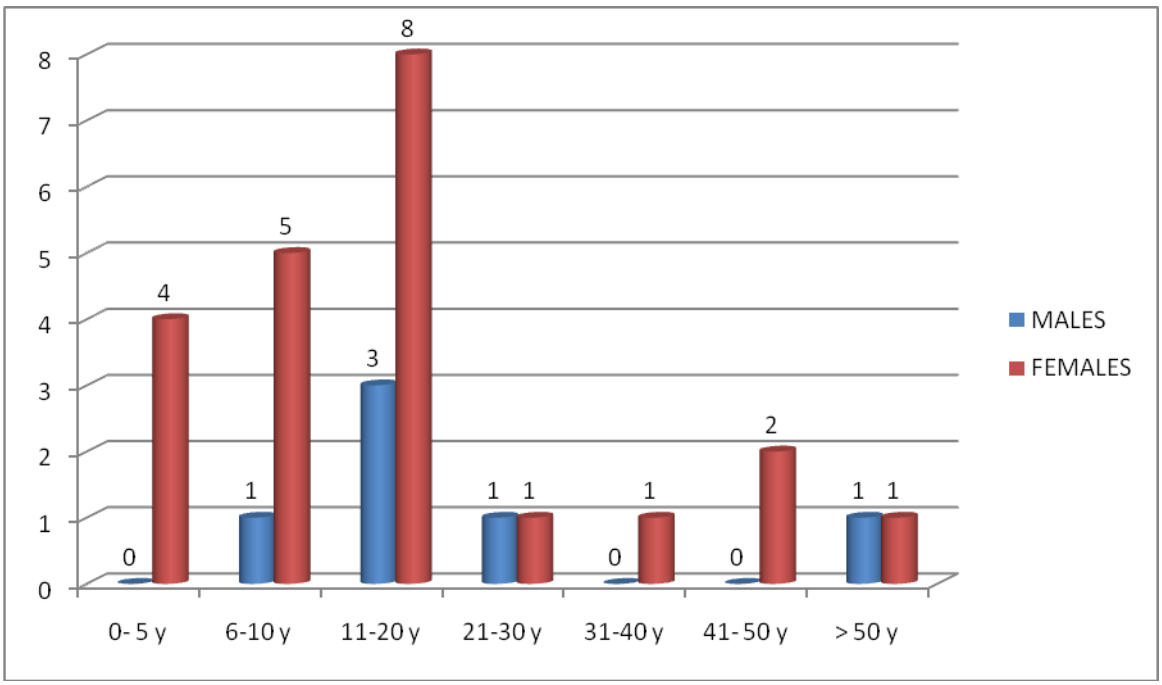


FIGURE 9 - AGE OF ONSET (LINEAR TYPE)

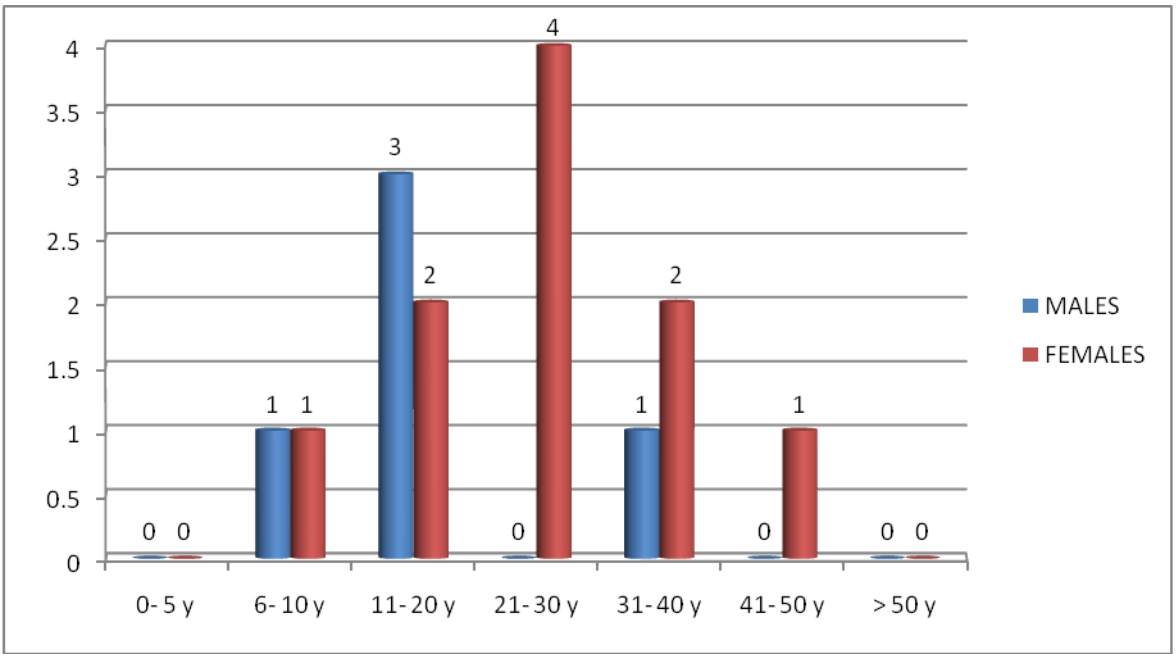


FIGURE 10- AGE OF ONSET (GENERALISED TYPE)

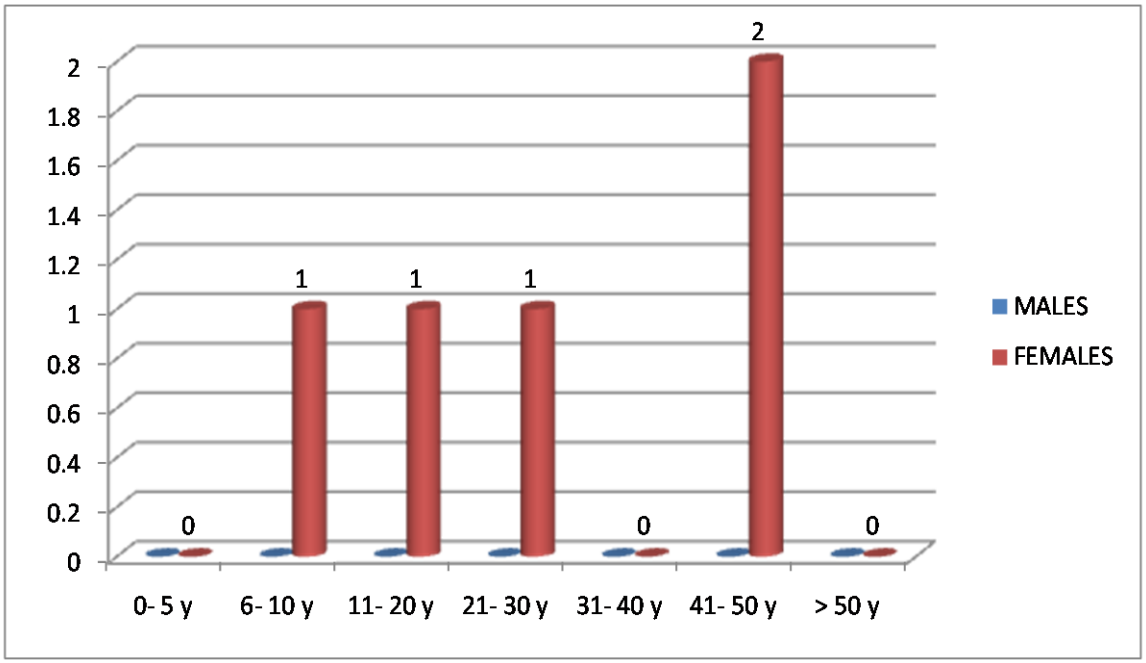


FIGURE 11- AGE OF ONSET (PANSCLEROTIC TYPE)

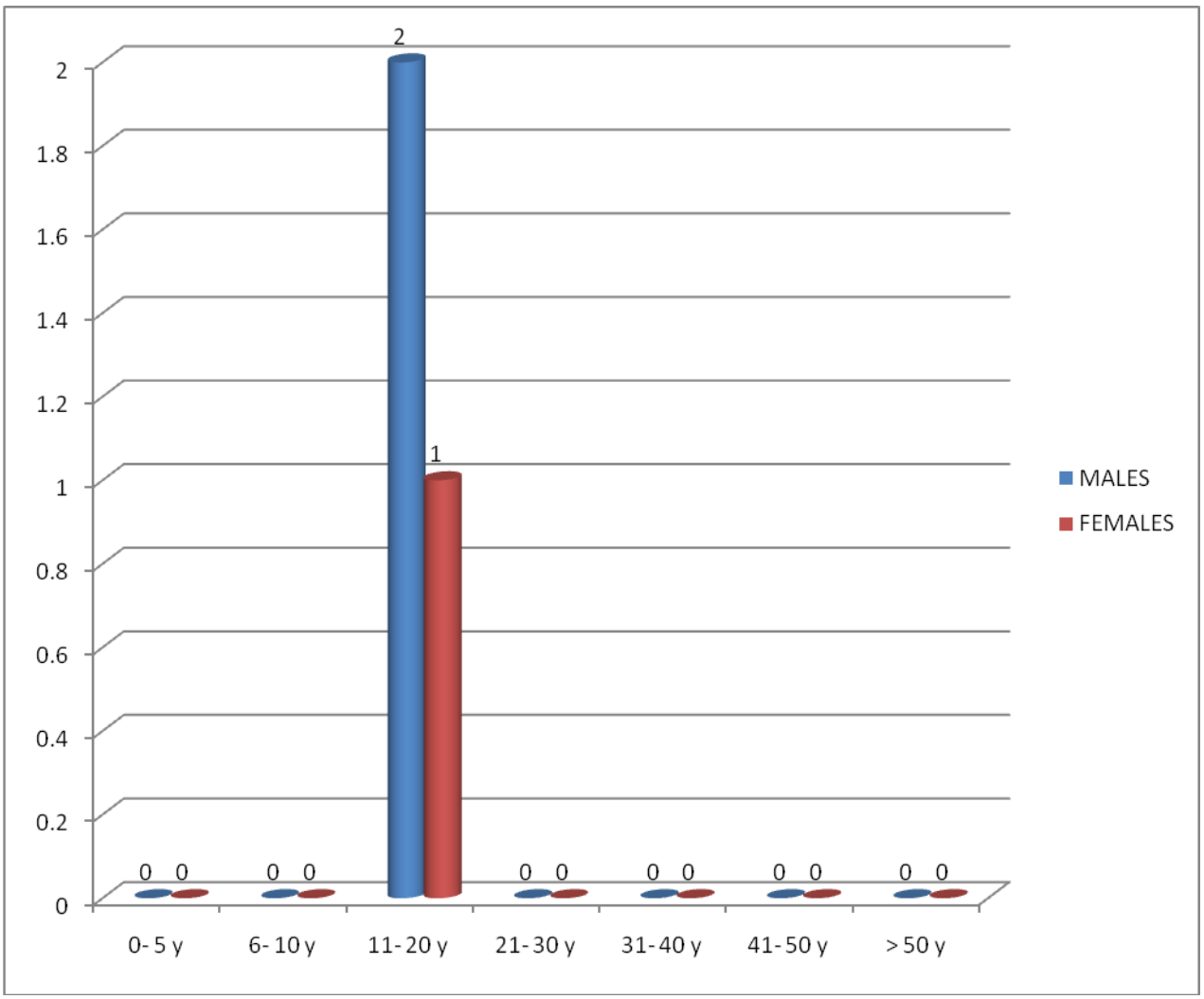


FIGURE 12- DURATION OF LESIONS

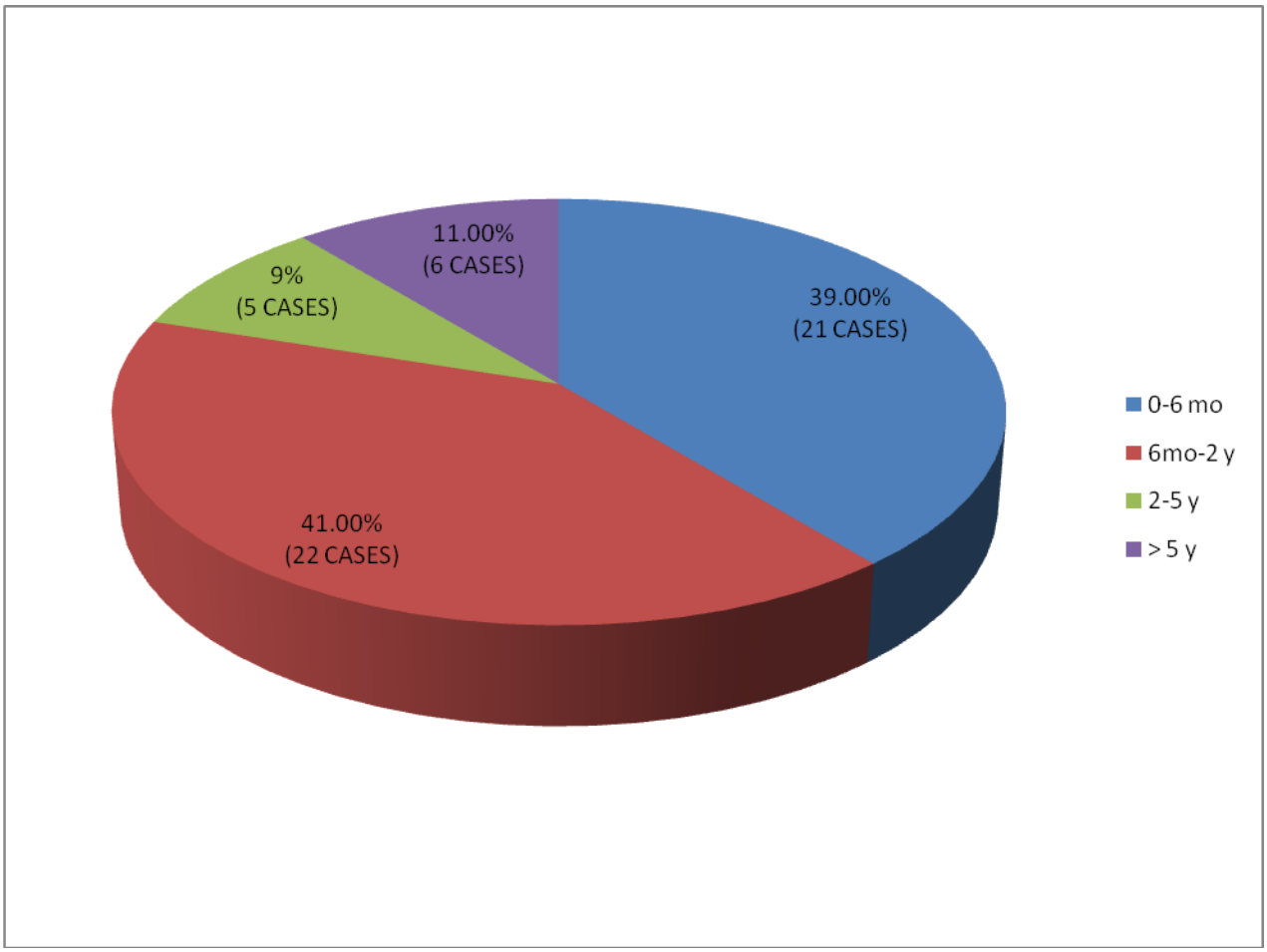


FIGURE 13- SITE WISE DISTRIBUTION-SINGLE SITE

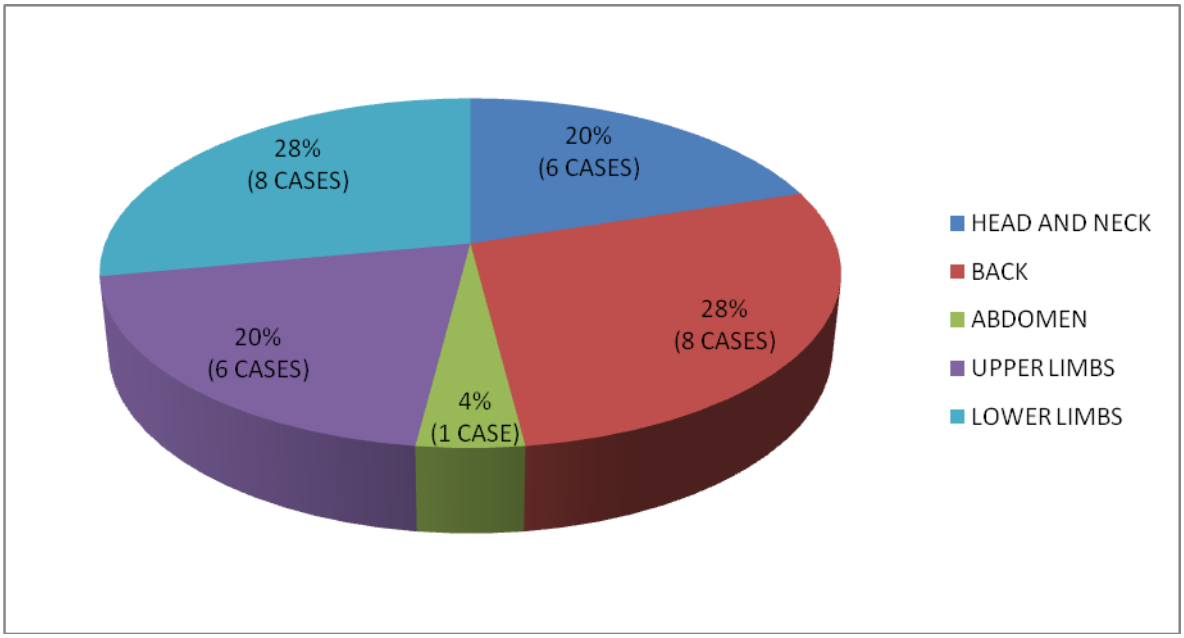


FIGURE 14- SITE WISE DISTRIBUTION- MULTIPLE SITES

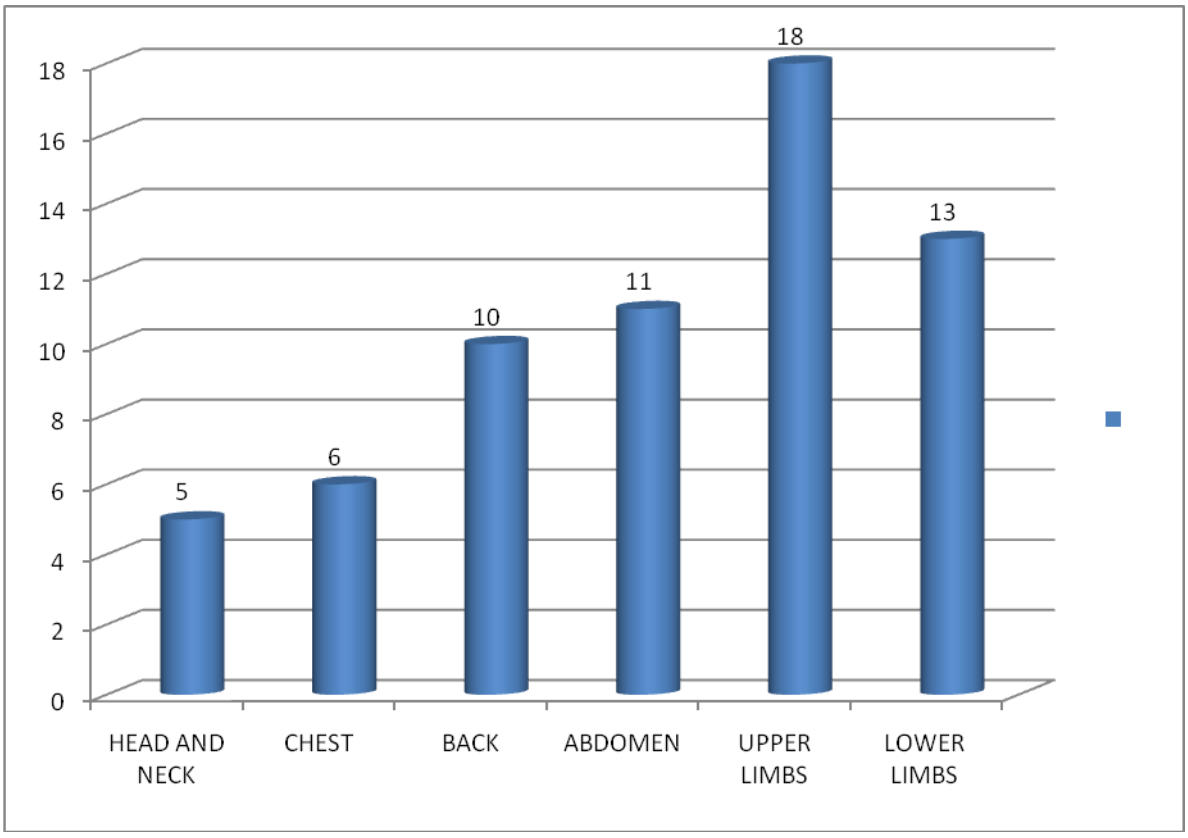


FIGURE 15- SITE WISE DISTRIBUTION (CIRCUMSCRIBED TYPE)

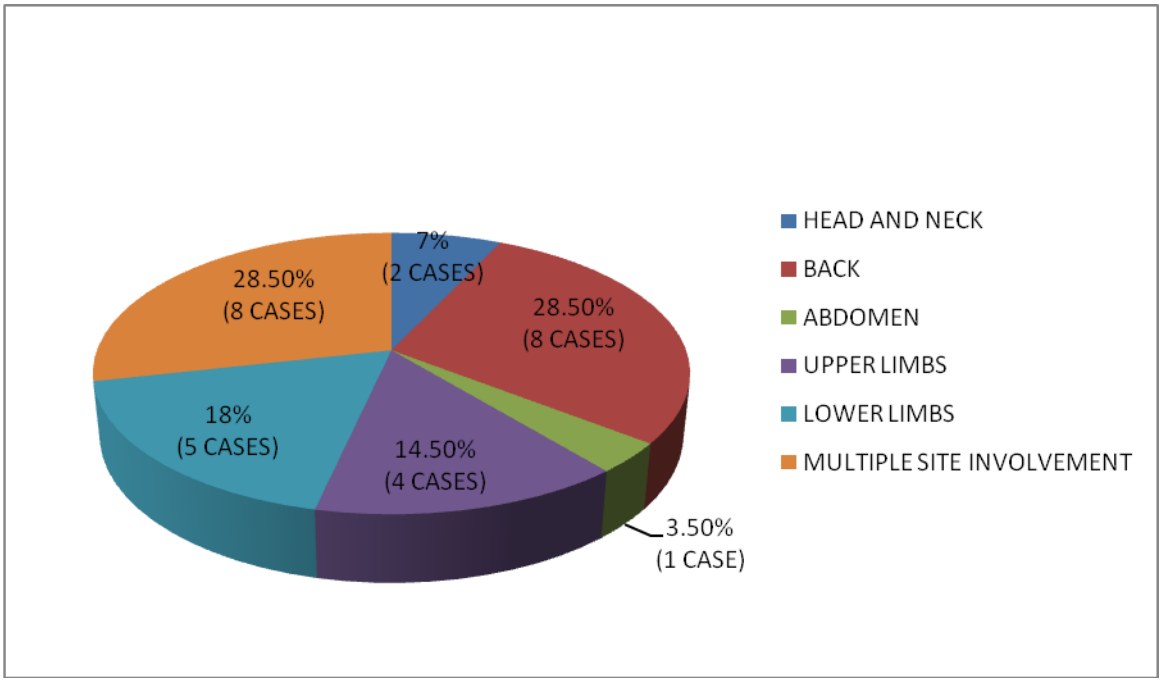


FIGURE 16- SITE WISE DISTRIBUTION (LINEAR TYPE)

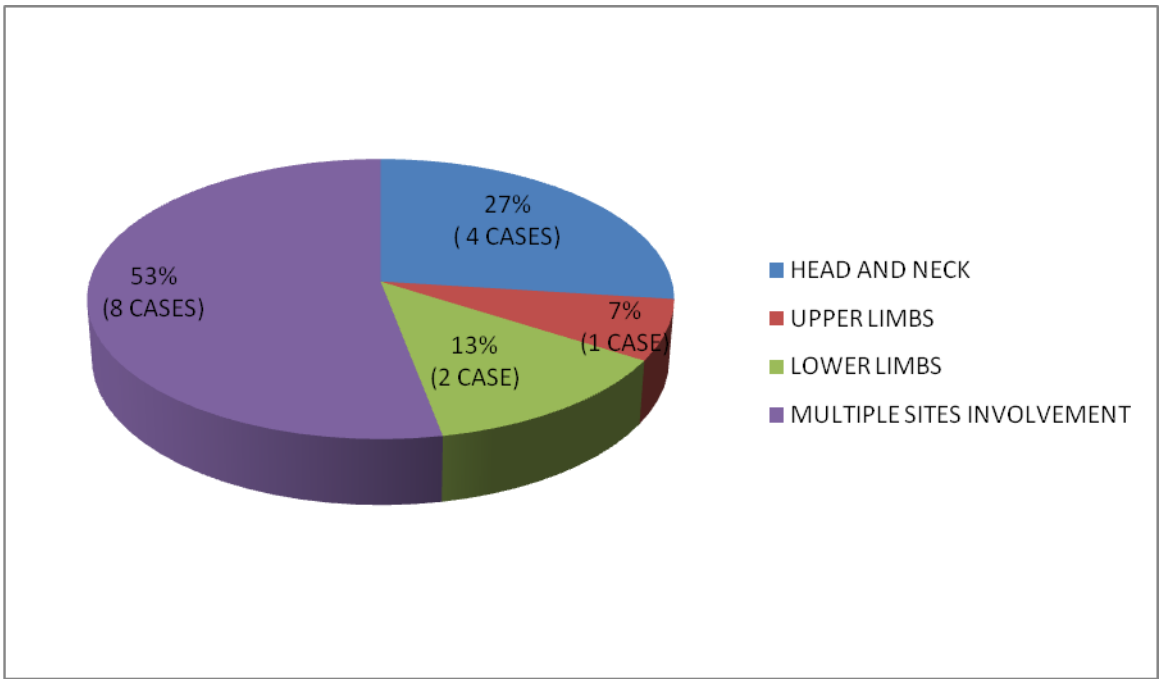


FIGURE 17- SYMPTOMS

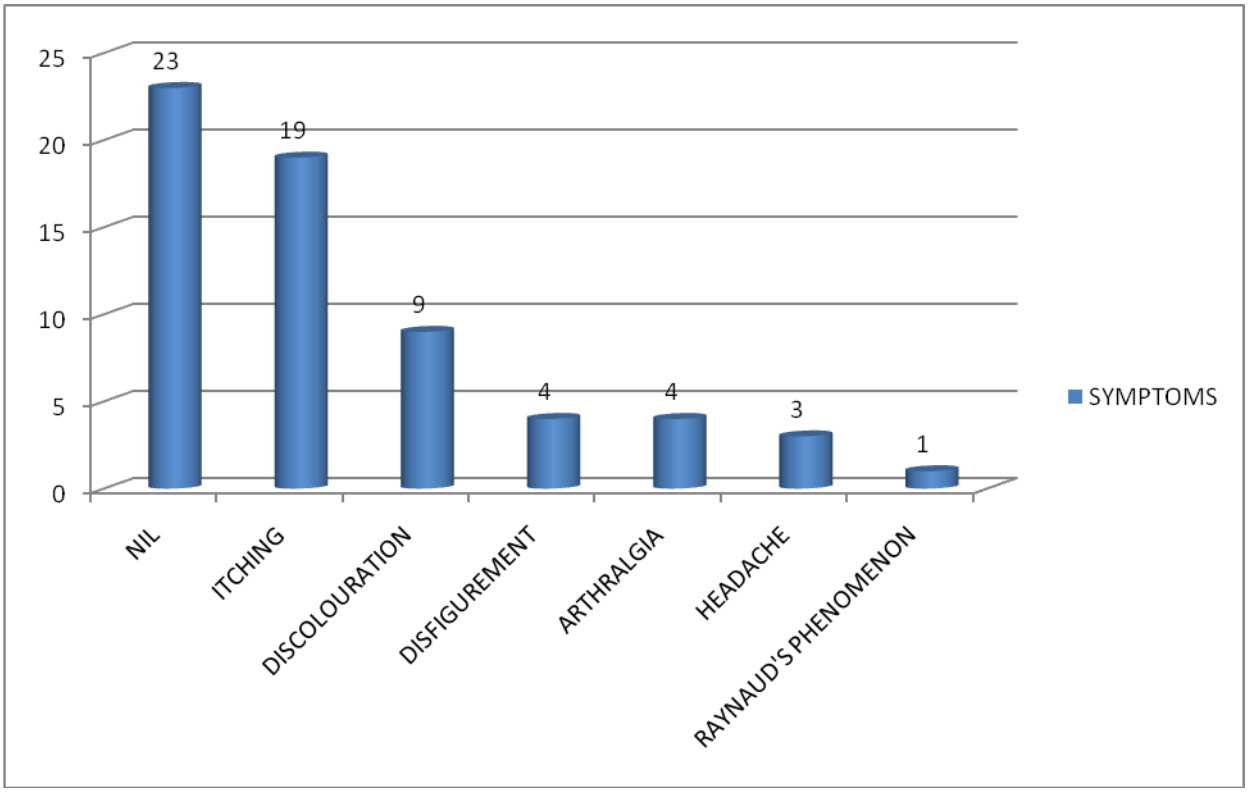


FIGURE 18- EVOLUTION OF LESIONS

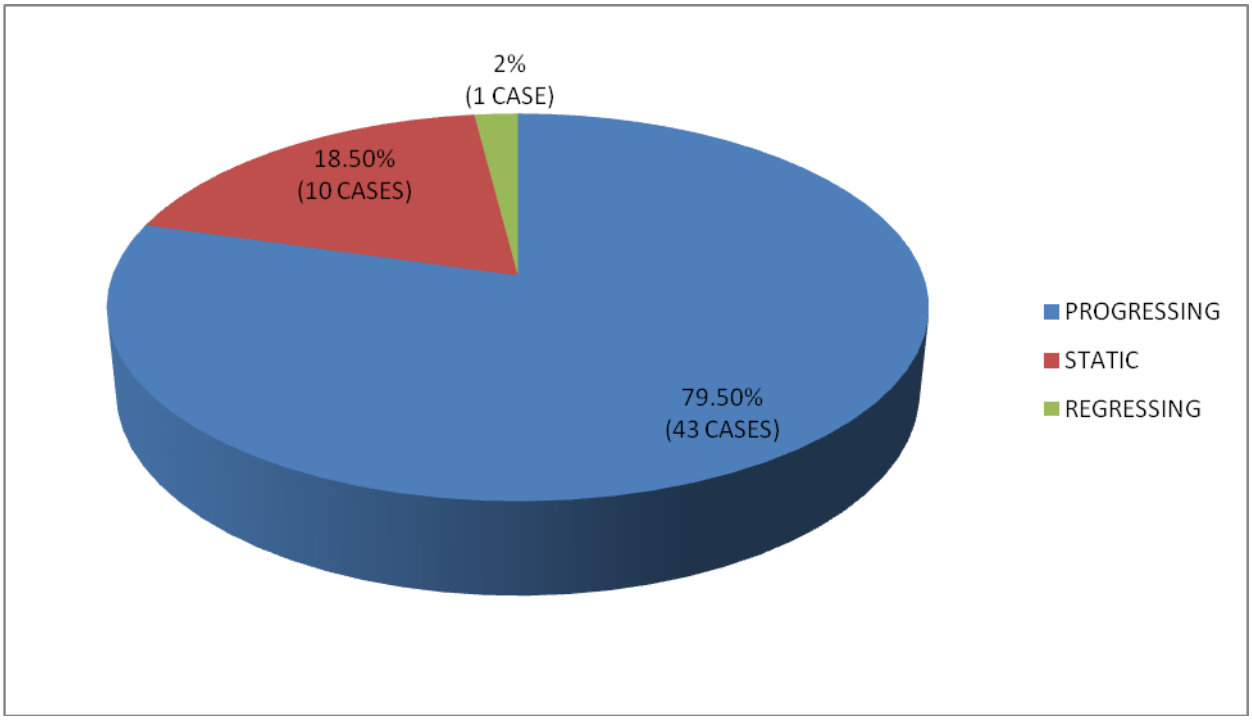


FIGURE 19- PRECIPITATING FACTORS

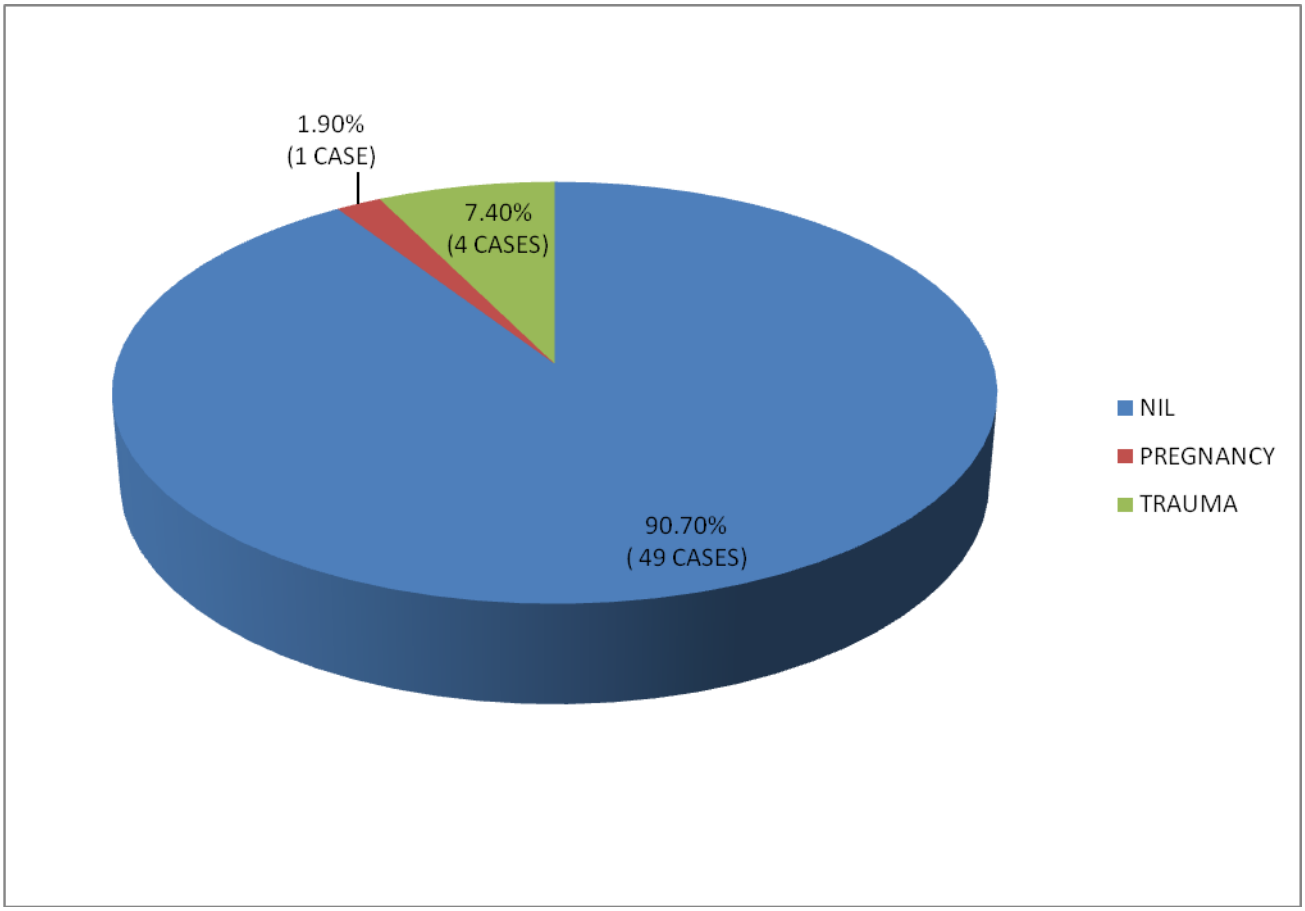


FIGURE 20- BIRTH HISTORY

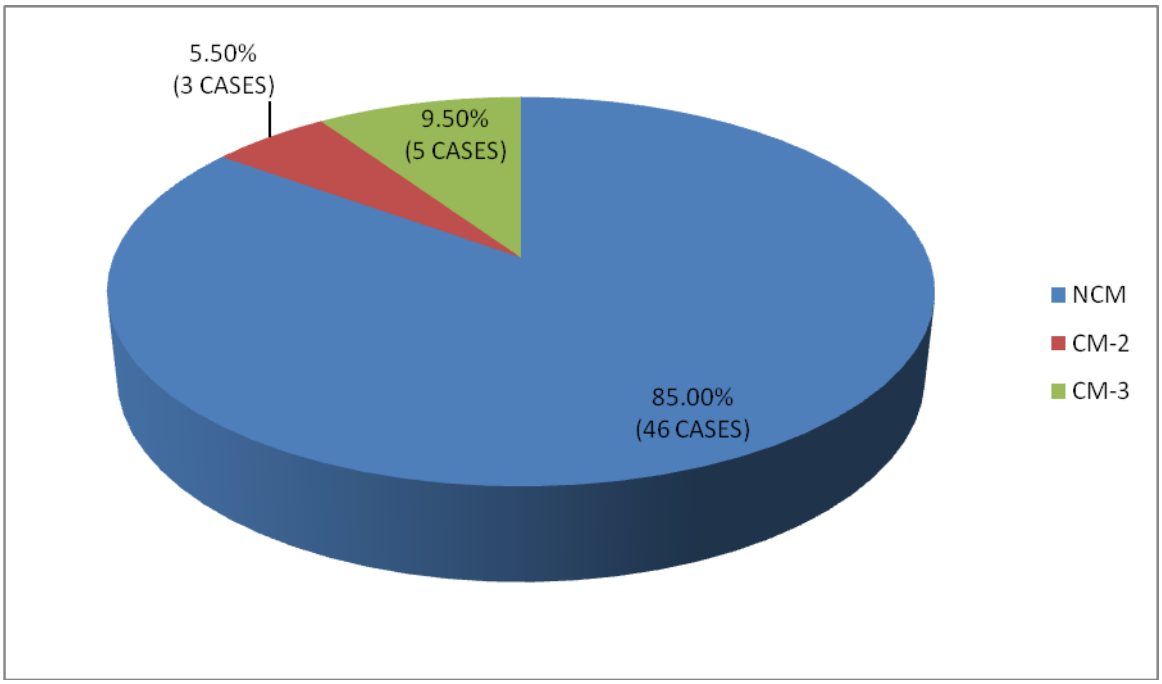


FIGURE 21- ASSOCIATED SYSTEMIC DISEASES

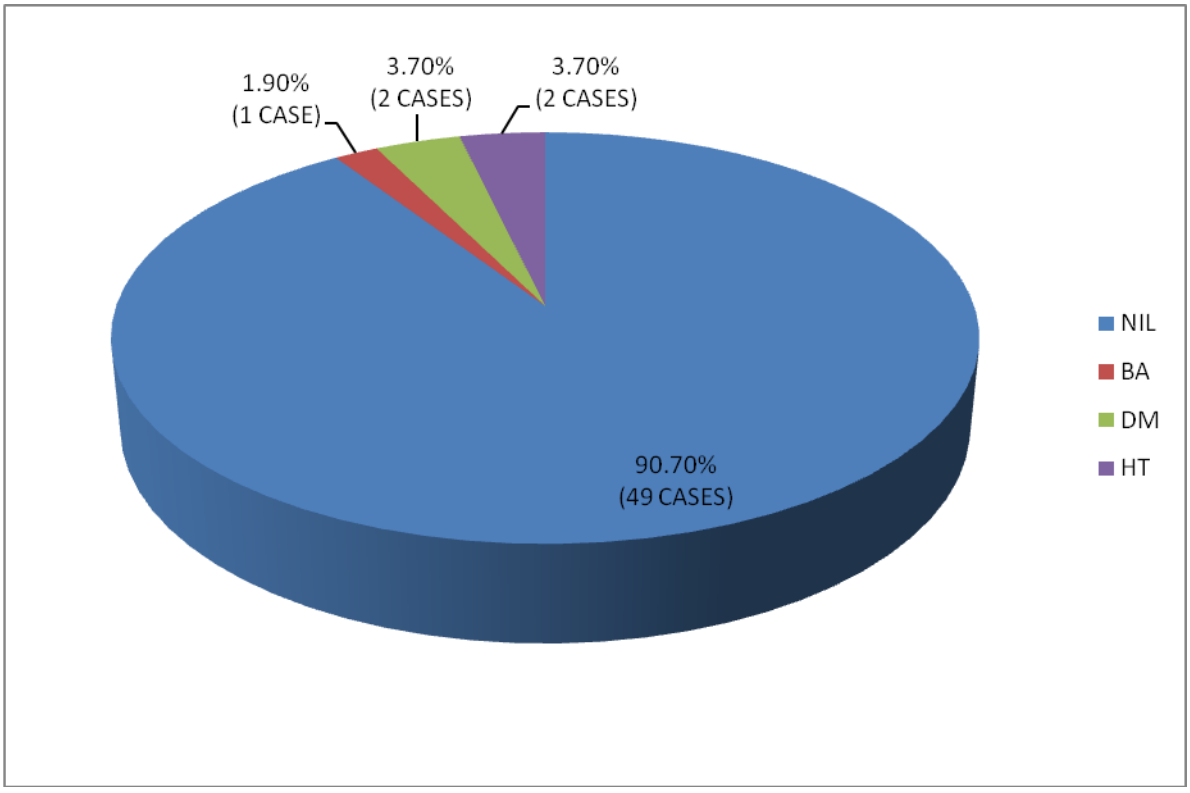


FIGURE 22- NUMBER OF LESIONS

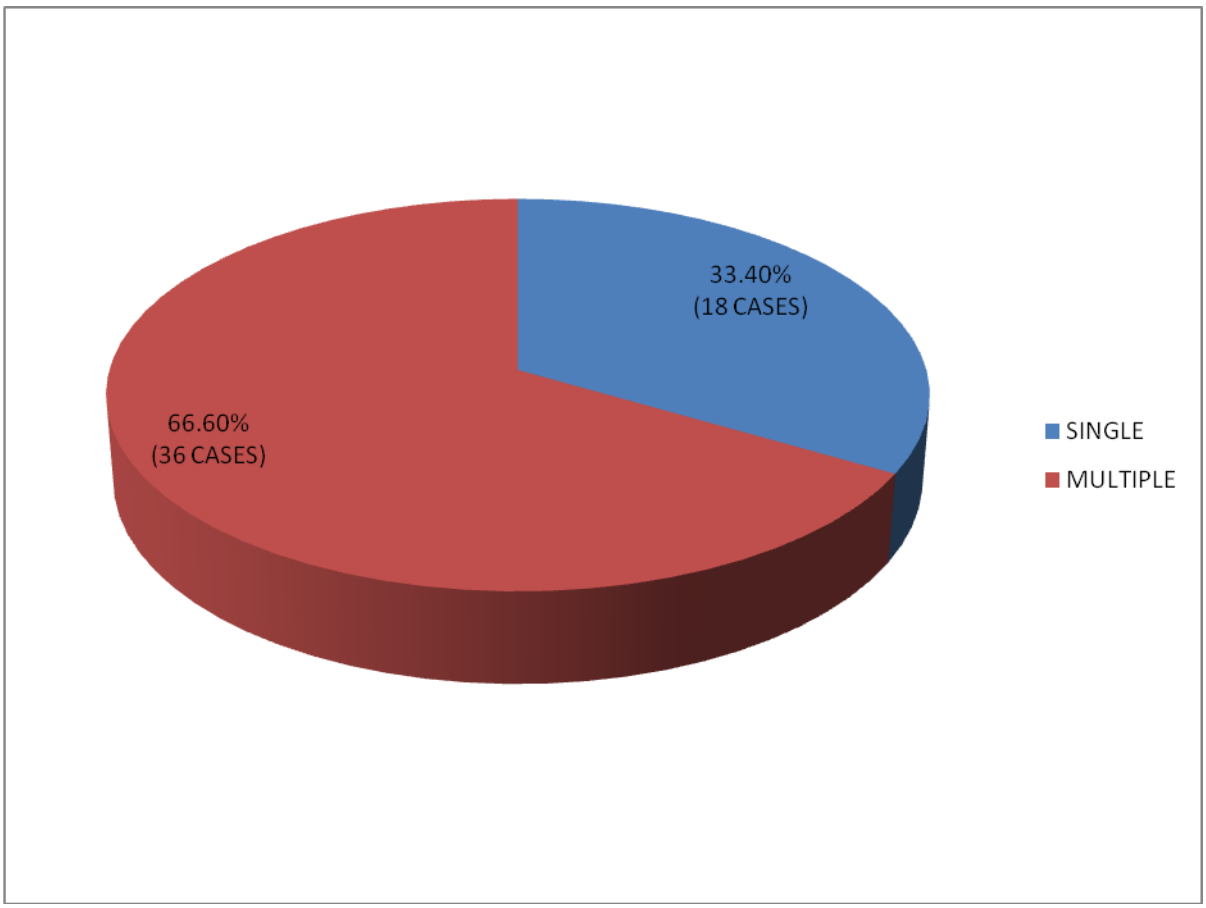


FIGURE 23- HEMIATROPHY

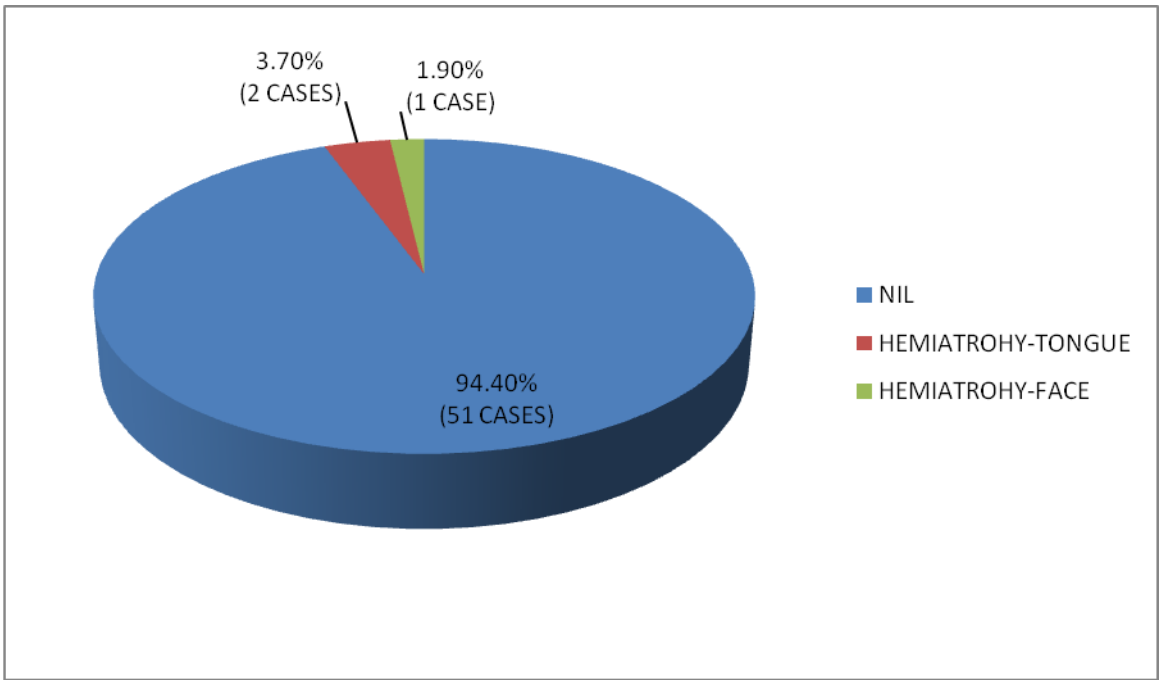


FIGURE 24- COMPLETE BLOOD COUNT

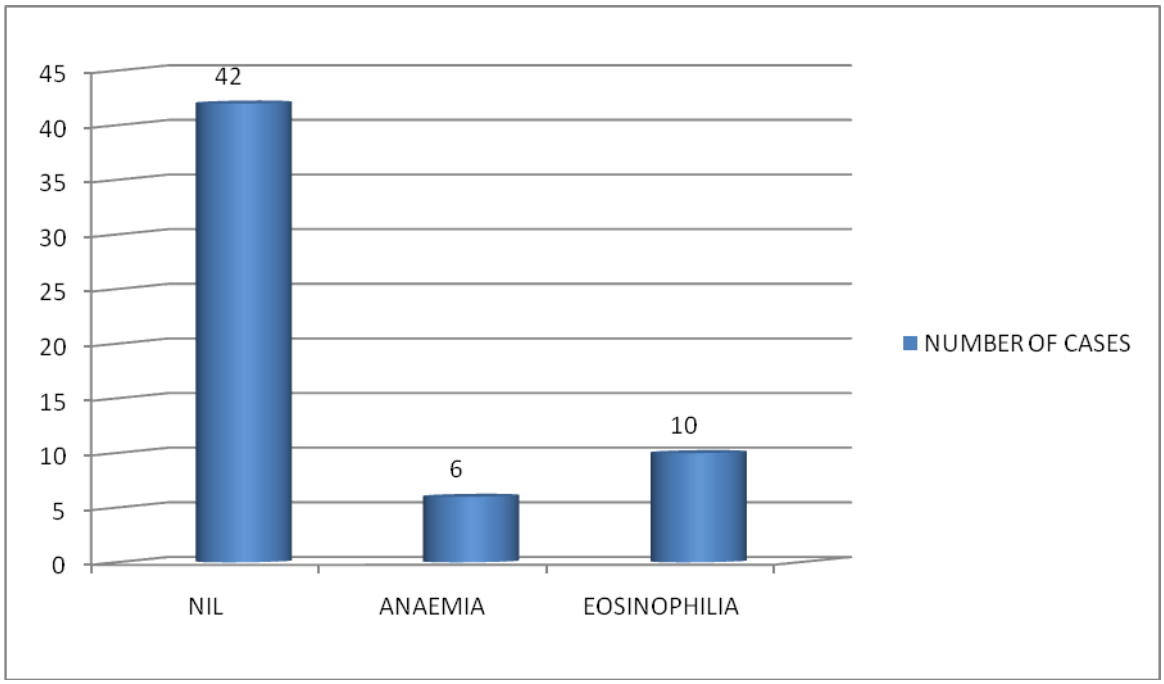


FIGURE 25- SITE OF BIOPSY

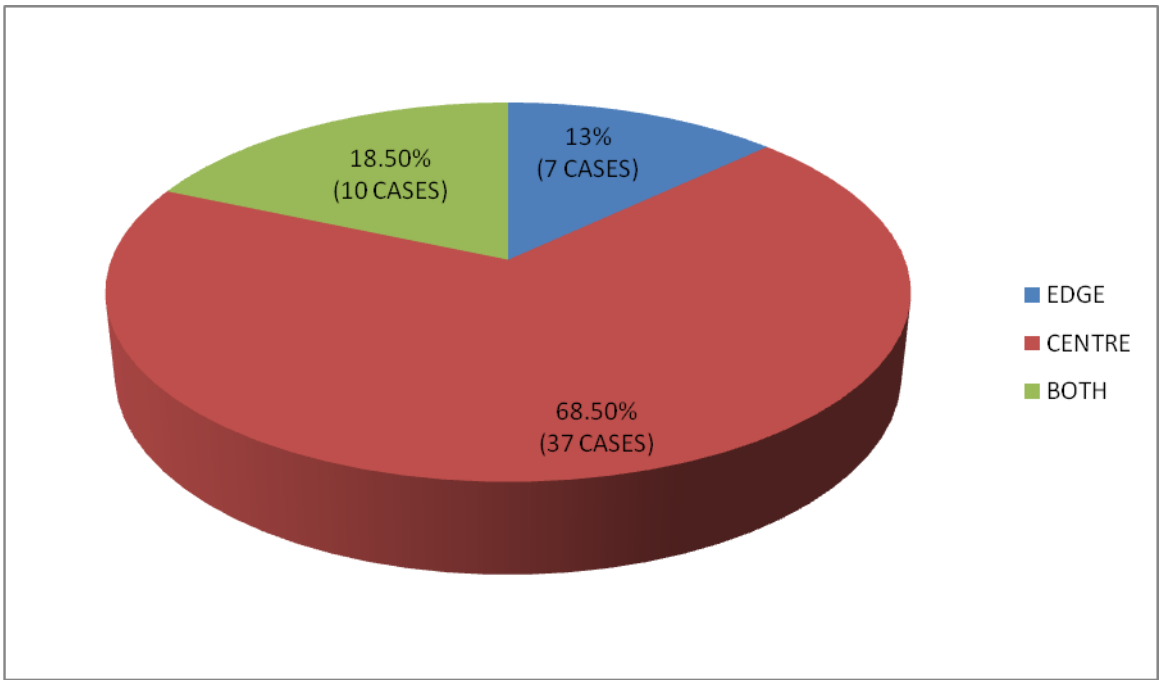


FIGURE 26-HISTOPATHOLOGICAL STAGE OF MORPHOEA

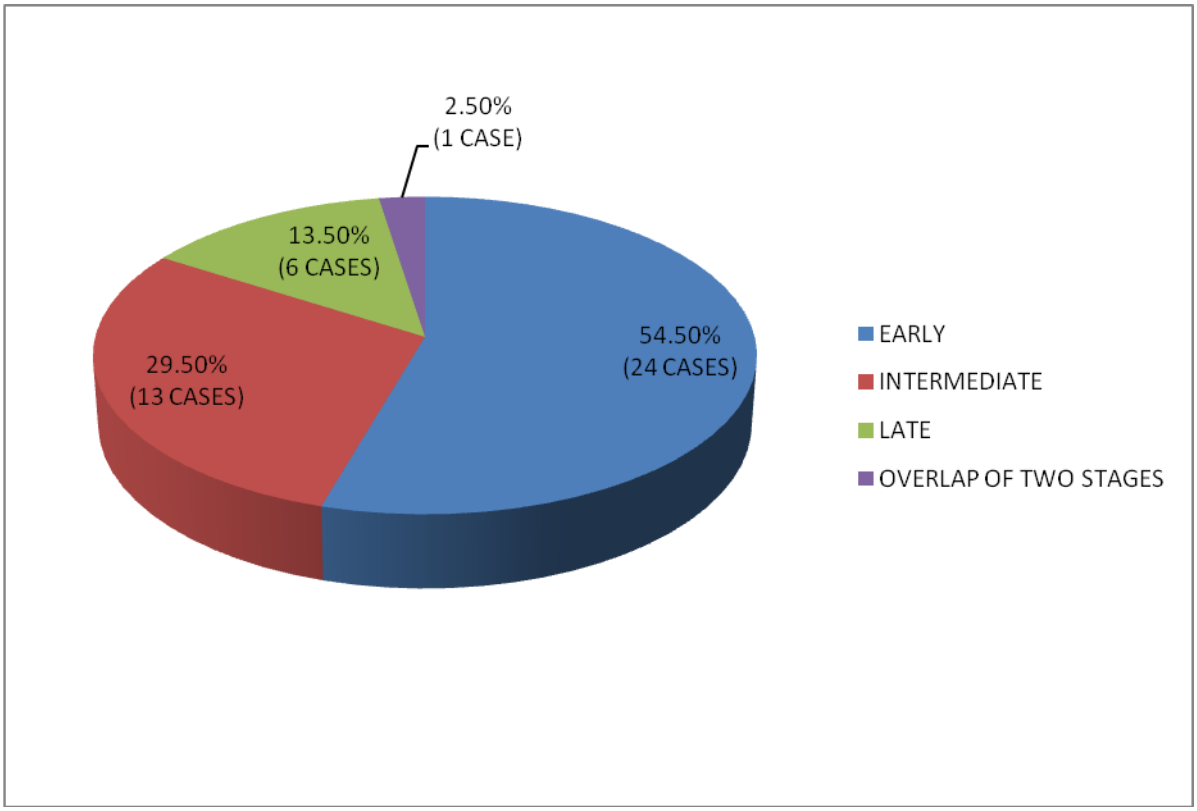


FIGURE 27- ASSOCIATED NAIL CHANGES

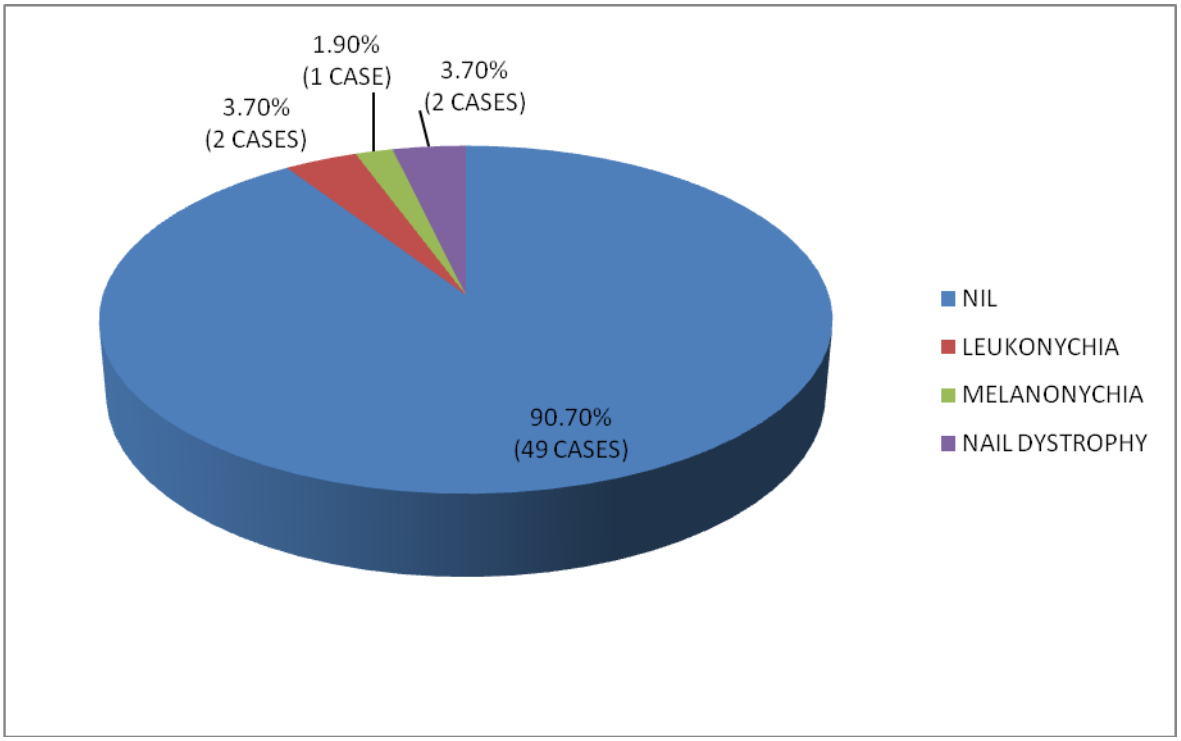
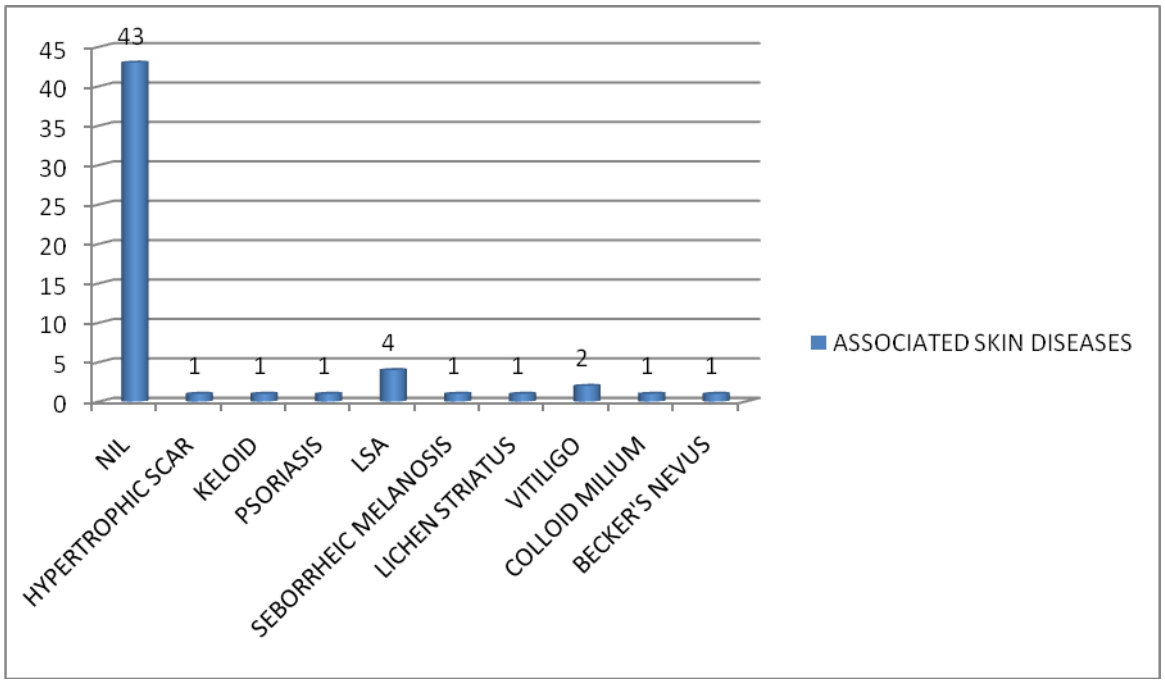


FIGURE 28- ASSOCIATED SKIN DISEASES



CIRCUMSCRIBED MORPHOEA

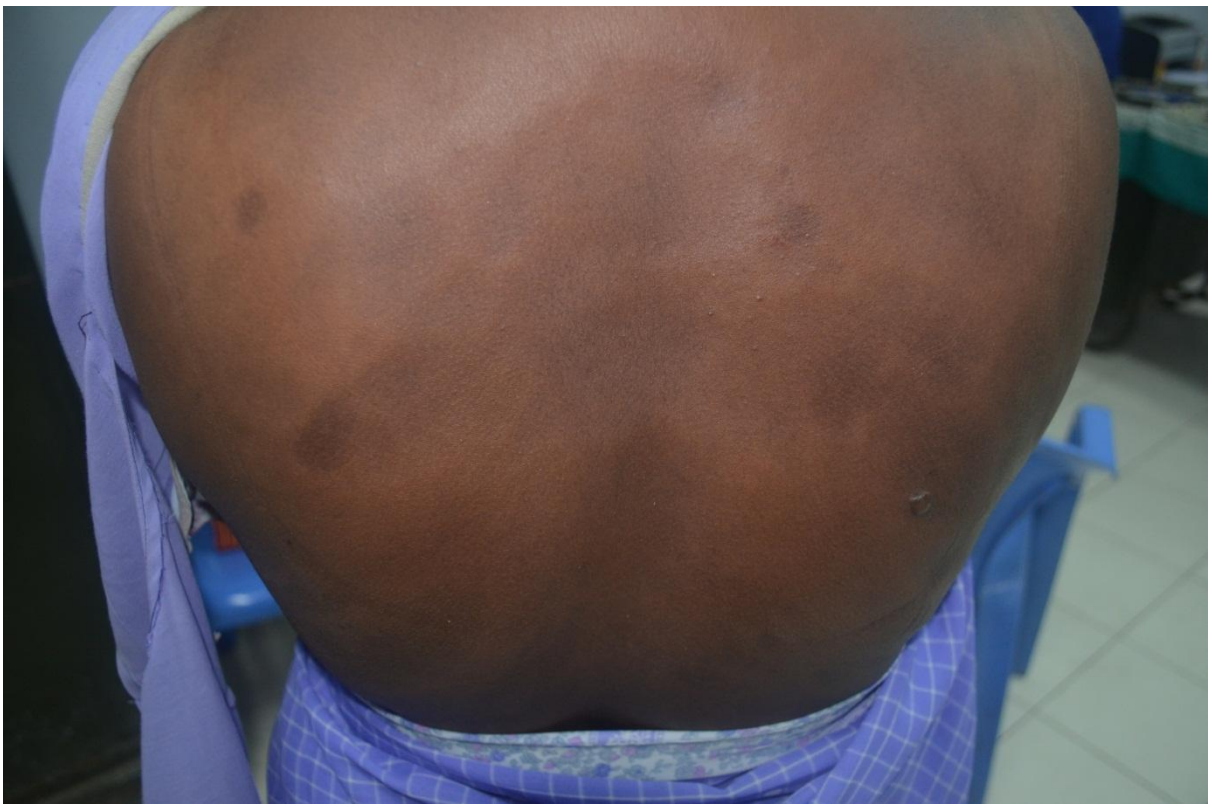
LINEAR MORPHOEA- EN COUP DE SABRE VARIANT

LINEAR MORPHOEA- TRUNK LIMB VARIANT

PANSCLEROTIC MORPHOEA

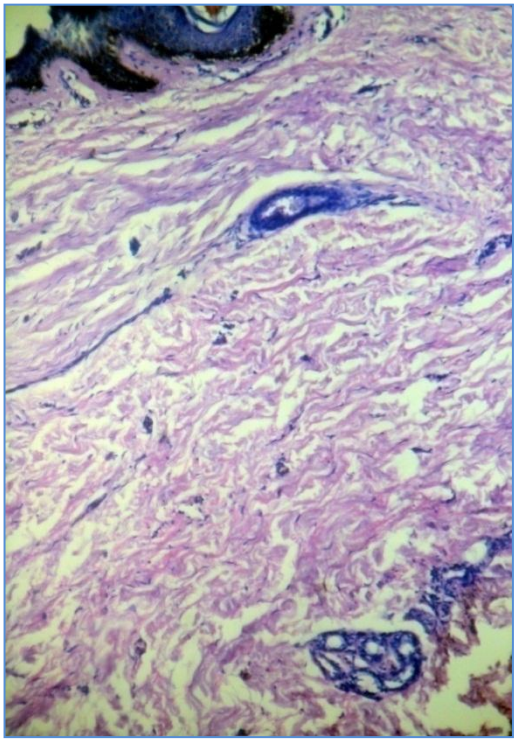
MIXED VARIANT- LINEAR WITH CIRCUMSCRIBED WITH EN COUP DE SABRE

GENERALISED MORPHOEA

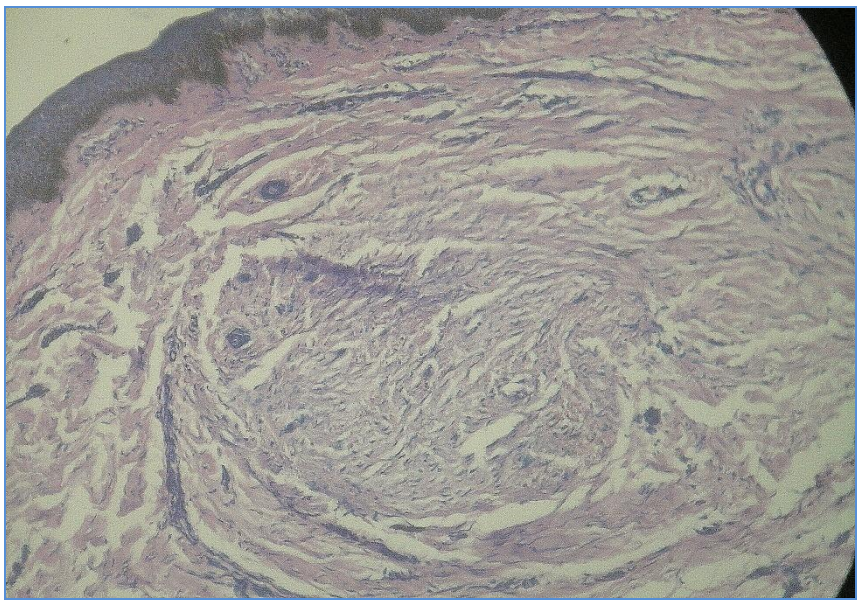


KELOIDAL MORPHOEA

MORPHOEA LESION

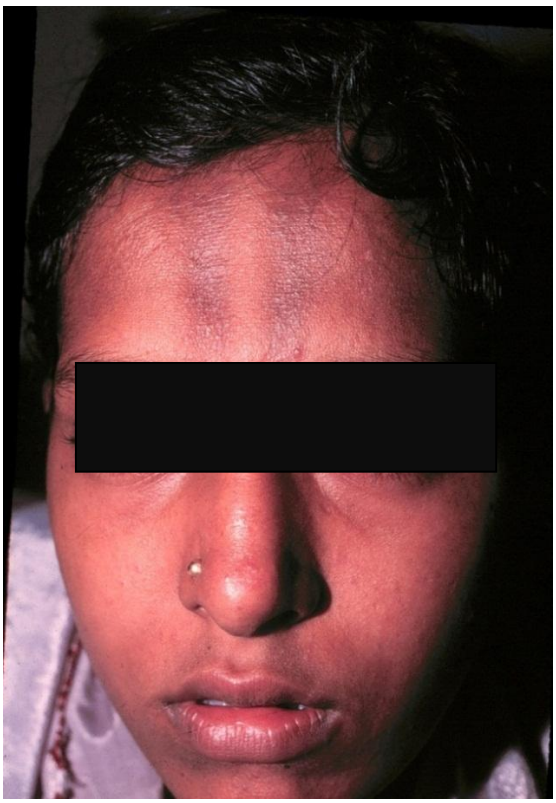


KELOIDAL LESION

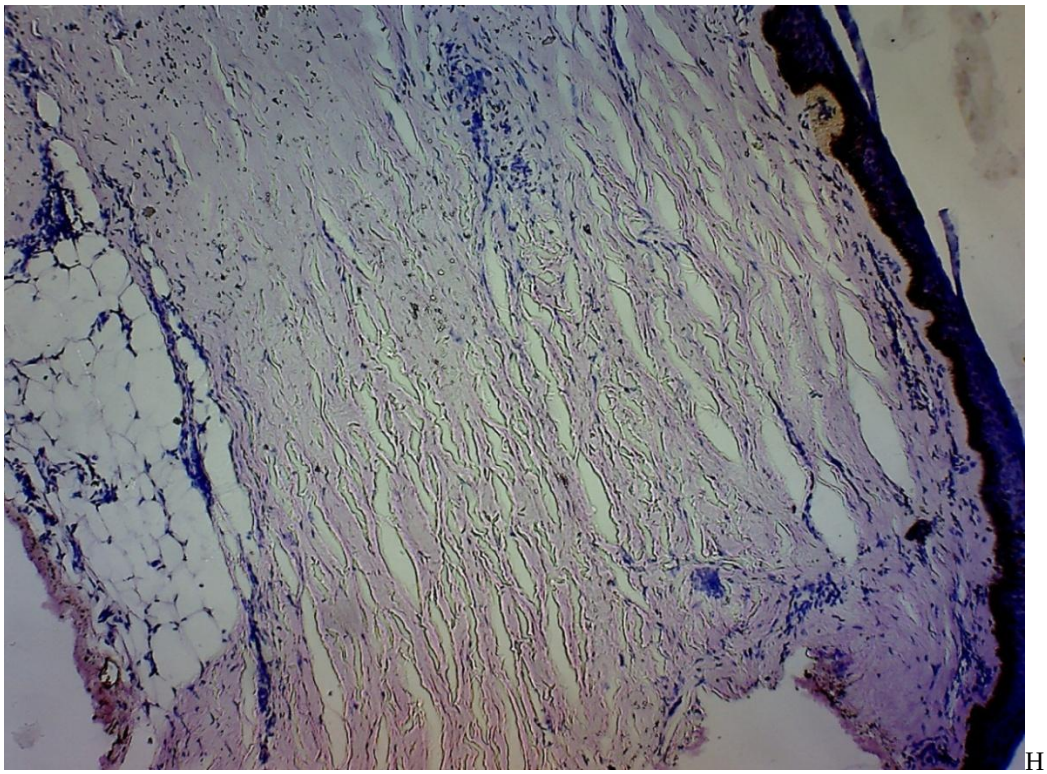


Circumscribed area of fibrosis amidst hyalinised, hypocellular collagen H & E, 10 X

BILATERAL EN COUP DE SABRE



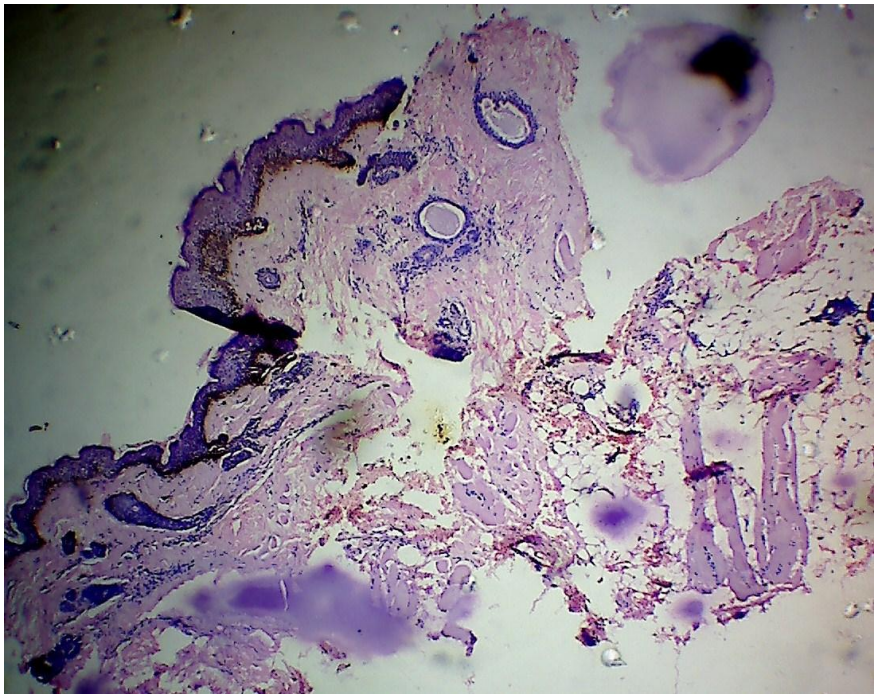
HISTOPATHOLOGY OF LINEAR MORPHOEA SHOWING EXTENSIVE AND DEEP INFILTRATE



H & E, 10 X

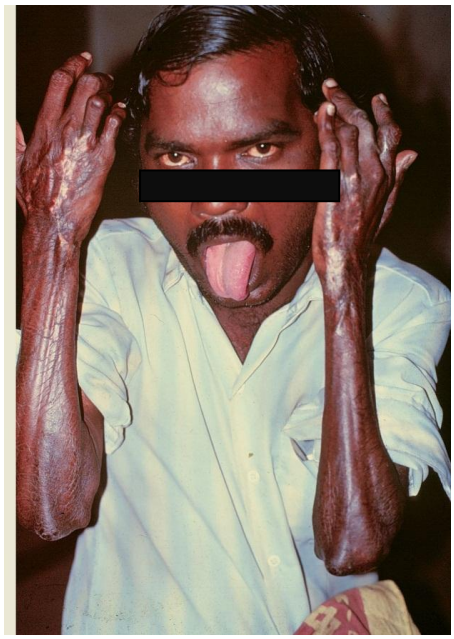
HEMIATROPHY OF FACE- CASE OF PARRY ROMBERG SYNDROME

HYALINISED COLLAGEN AND SPARSE PERIVASCULAR INFILTRATE IN THE DERMIS AND SUBCUTIS



H & E, 10 X

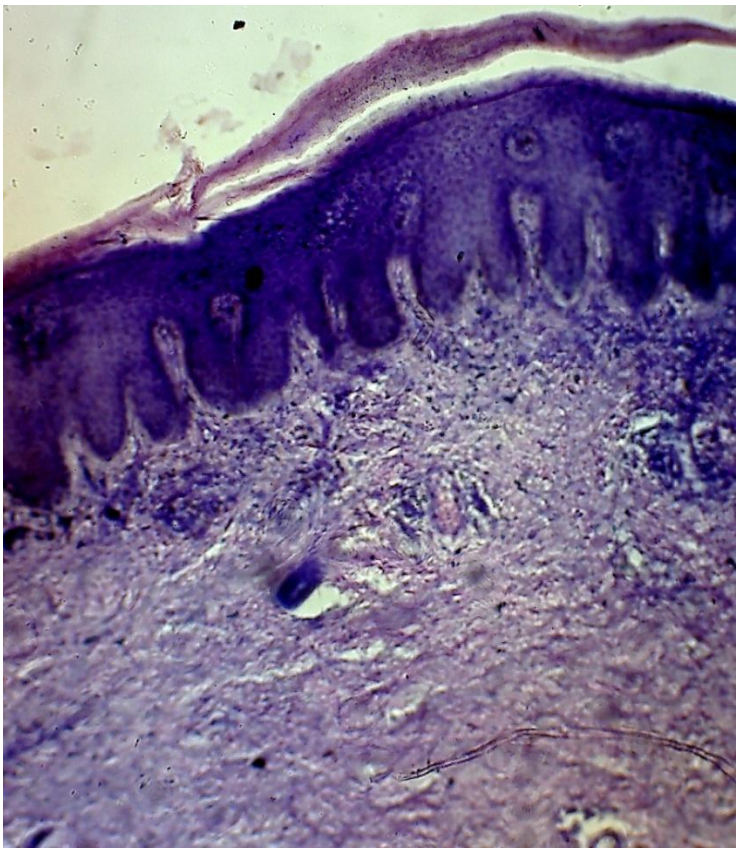
PANSCLEROTIC MORPHOEA WITH HEMIATROPHY OF TONGUE



PANSCLEROTIC MORPHOEA WITH ATROPHY OF LOWER LIMB

COLOCALIZATION OF PSORIASIS OVER MORPHOEA PLAQUE IN A CASE OF PANSCLEROTIC MORPHOEA

OVERLYING EPIDERMIS SHOWING FEATURES OF PSORIASIS



H & E, 10 X

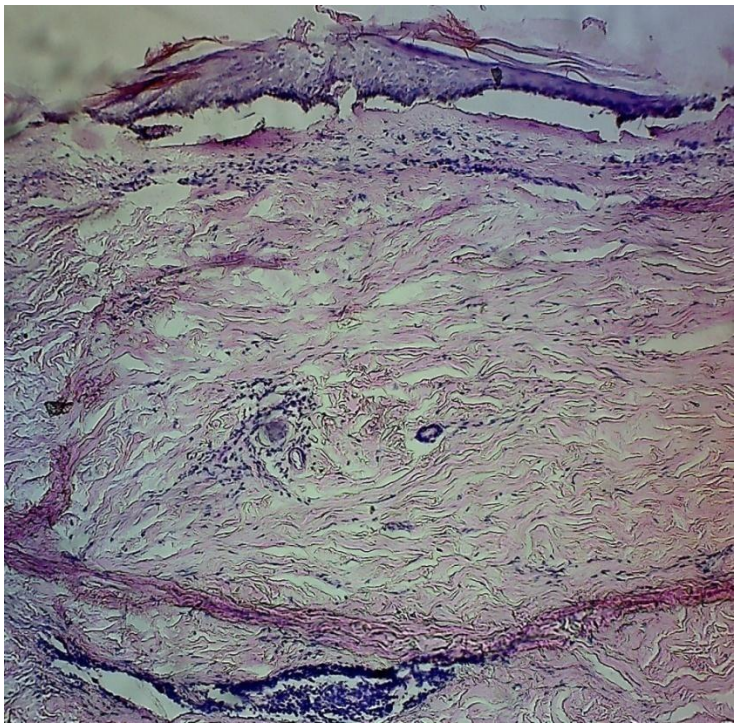
CIRCUMSCRIBED MORPHOEA

ASSOCIATED LICHEN STRIATUS IN THE SAME PATIENT

LINEAR MORPHOEA- TRUNK LIMB VARIANT

ASSOCIATED LICHEN SCLEROSUS ET ATROPHICUS IN THE SAME PATIENT

HISTOPATHOLOGY OF LSA LESION



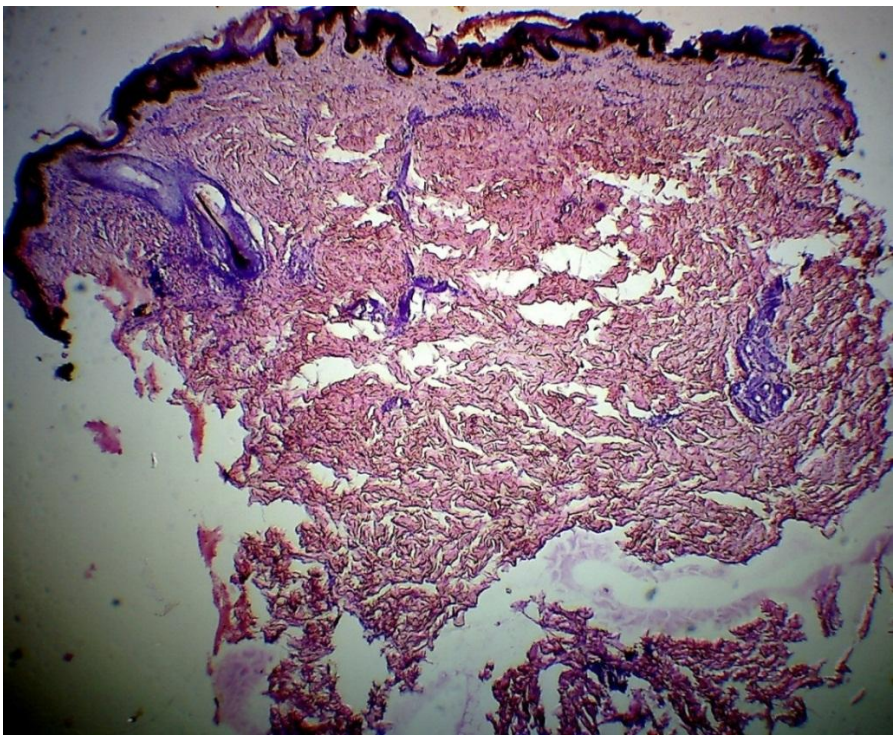
H & E, 10 X

ASSOCIATED VITILIGO IN A CASE OF LINEAR MORPHOEA

LINEAR MORPHOEA- TRUNK LIMB VARIANT

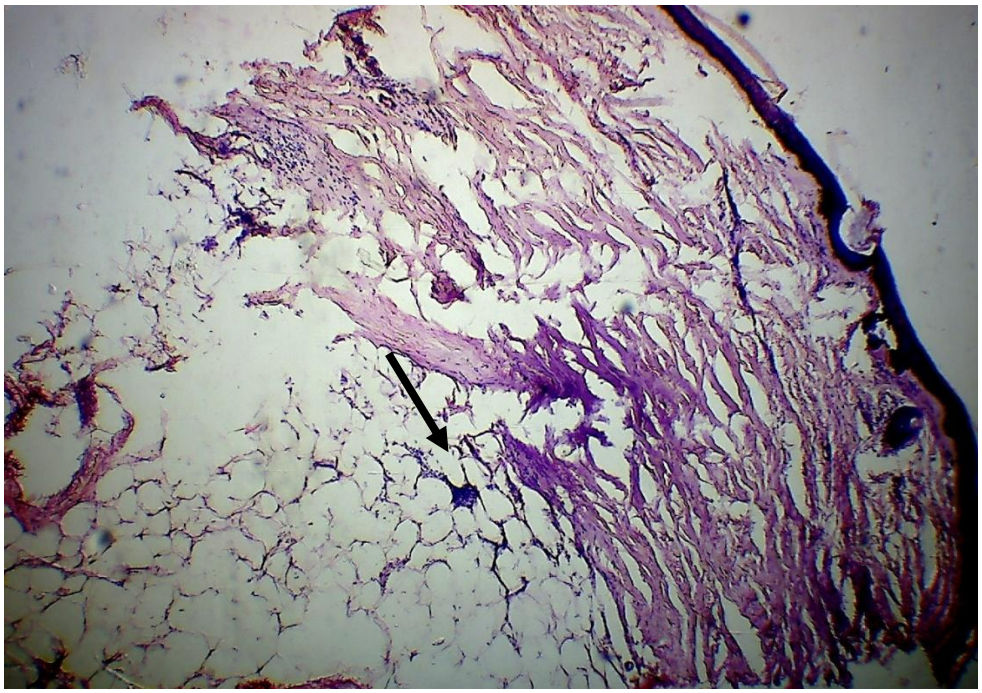
ASSOCIATED BECKER'S NEVUS IN THE SAME PATIENT

EARLY STAGE



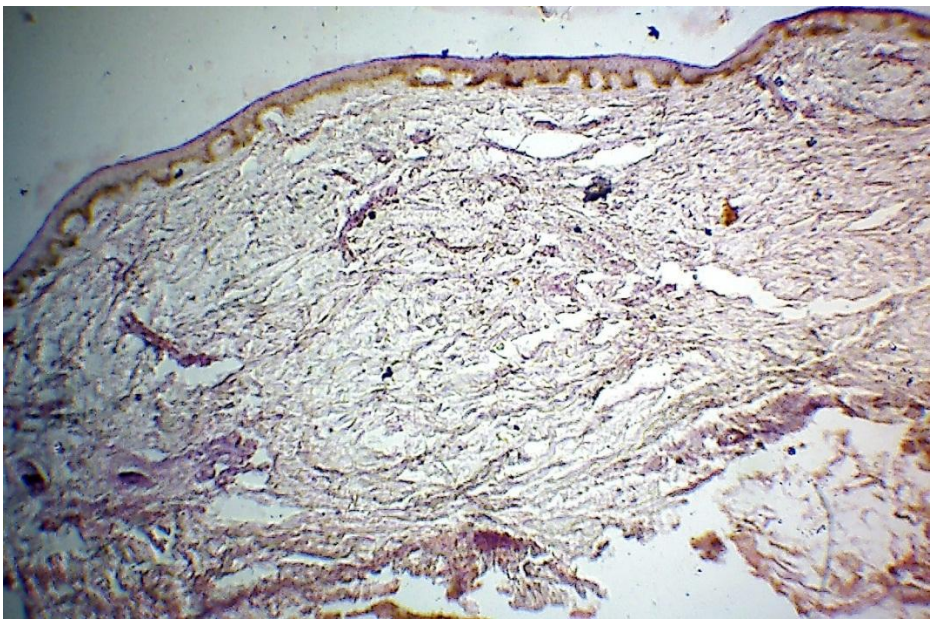
Hyalinised hypocellular collagen with sparse perivascular infiltrate in upper dermis H & E, 10 X

INTERMEDIATE STAGE



Infiltrate extending into subcutis H & E, 10 X

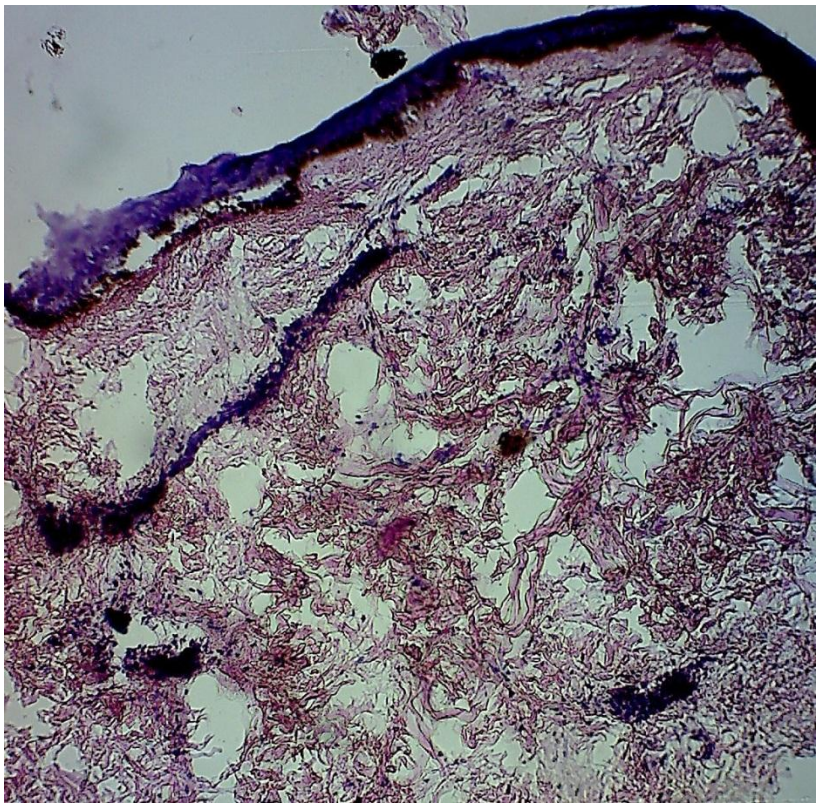
LATE STAGE



Features of classical morphoea with no significant infiltrate

H & E, 10 X

CASE OF CIRCUMSCRIBED MORPHOEA SHOWING FEATURES OF EARLY STAGE ALONG WITH A SUBEPIDERMAL SPACE



H & E, 10 X

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PROFORMA

CASE NO.: **DATE**
NAME-
AGE/SEX **OCCUPATION**

ADDRESS

PHONE NO-
CHIEF COMPLAINTS-

SKIN LESIONS
DURATION: **AGE OF ONSET**:
SITE
Face: Scalp :
UL LL
Chest Back of trunk
Abdomen: Lower/upper Buttocks Genitals
NO OF LESIONS
SYMPTOMS
Asymptomatic Discolouration Disfigurement Itching Pain

Deformity

OTHERS- Arthralgia Rec colicky abdominal pain Headache

Discolouration on cold exposure Lumbar pain Seizures

ANY OTHER-

EVOLUTION/REGRESSION
A)PROGRESSING
1) Increase in size
2) New lesions
B) STATIC
C)REGRESSING
PRECIPITATING FACTORS
Trauma
Immobilisation

Vaccination BCG DPT MMR
Other injections B12 Vitamin K
H/O Herpes zoster
H/O Radiotherapy
Pregnancy
Infection
Exposure to chemicals
Silicon implants
Drugs- Penicillamine
Carbidopa
Bromocriptine
Anti epileptic drugs

PAST H/O-
DM HT TB BA
Other skin diseases
Others

FAMILY H/O-
Similar lesions
Other skin lesions
Other diseases

TREATMENT H/O:

GENERAL EXAMINATION:

SYSTEMIC EXAMINATION
CVS
RS
CNS
P/A

OCULAR EXAMINATION:
Lid ptosis:
Enophthalmos
Heterochromia iris:

MUSCULOSKELETAL EXAMINATION:

DERMATOLOGICAL EXAMINATION:

No of lesions Single Multiple Numerous
Shape Oval Round Linear Other
Size
Border Well circumscribed Ill circumscribed
Colour Plaque Margin
Consistency Indurated Non indurated
Surface Shiny Hair
Atrophy
Sensation
Attachment to underlying structures Subcutis Muscle
Bone
Others
Tenderness

SCALP

HAIR

ORAL CAVITY AND DENTITION

GENITALIA

PALMS AND SOLES

NAILS

DIAGNOSIS

INVESTIGATIONS:

COMPLETE HAEMOGRAM-
Hb
TC
DC
ESR
PERIPHERAL SMEAR

BLOOD SUGAR
UREA
CREATININE

LFT

X RAY LOCAL PART SPINE

BIOPSY-
Date-
Site-
Early or Late lesion

Special stain

Report and number

OPHTHALMOLOGY OPINION:

NEUROLOGY OPINION:

KEY TO MASTER CHART

A	-	Anaemia
Abn	-	Abnormal
Ar	-	Arthralgia
At	-	Atrophic
B	-	Both
BA	-	Bronchial asthma
BN	-	Becker's nevus
C	-	Circumscribed
ce	-	Centre
CM	-	Colloid milium
CM-2	-	2nd degree consanguineous marriage
CM-3	-	3rd degree consanguineous marriage
CO	-	Contractures
co and	-	Compatible with morphoea i.e hyalinised, homogenous hypocellular collagen with high uptake of eccrine glands
DC	-	Discolouration
DFG	-	Disfigurement
DM	-	Diabetes mellitus
E	-	Eosinophilia
ear	-	Early
ear-int	-	Early to intermediate
ed	-	Edge

F - Female

G - Generalised

H - Headache

HA-F - Present over face

HA-T - Present over tongue

HT - Hypertension

HS - Hypertrophic scar

I - Itching

Infl - Infiltrate

Infl-PA - Periadnexal infiltrate

Infl-PV - Perivascular infiltrate

Infl-PA, PV - Both periadnexal and perivascular infiltrate

Int - Intermediate

int-lat - Intermediate to Late

K - Keloid

kel - Compatible with keloid i.e whorled, nodular mass of collagen interspersed with fibroblasts

L - Left

L(HV-E) - Linear (Head variant- en coup de sabre)

L(HV-P) - Linear (Head variant- Parry Romberg syndrome)

L(TL) - Linear (Trunk/limb variant)

LNY - Leukonychia

LS - Lichen striatus

LSA - Lichen sclerosus et atrophicus

M - Male

M (L-C) - Mixed (Linear- Circumscribed)

MNY - Melanonychia

mo - Months

Mu - Multiple

n - Normal

N - Nil

NA - Not applicable

NCM - Non consanguineous marriage

ND - Nail dystrophy

NI - No infiltrate

O(K) - Others (Keloidal)

p - Present

p-B - Present on both sides

pig - Pigmented

p-L - Present on left side

p-R - Present on right side

p-Li - Present over limbs

pr - Progressing

Preg - Pregnancy

p-R - Present on right side

Ps - Psoriasis

PSM - Pansclerotic

r - Regressing

R	-	Right
RP	-	Raynaud’s phenomenon
s	-	Static
S	-	Single
SEC	-	Subepidermal cleft
SM	-	Seborrheic melanosis
Tr	-	Trauma
V	-	Vitiligo
VL	-	Variable loss
y	-	Years

Dept. of Dermatology.
3 copies

Ref. No. 00216 /E4/3/2011 Govt.Rajaji Hospital,Madurai.20.
Dated: 01.2012

Institutional Review Board / Independent Ethics Committee.
Dr. A. Edwin Joe, M.D (FM), BL.,
Dean, Madurai Medical College & 2521021 (Secy)
Govt Rajaji Hospital, Madurai 625020.
Convenor
grhethicssecy @gmail.com.

Sub: Establishment-Govt. Rajaji Hospital, aMadurai-20-
Ethics committee-Meeting Agenda-communicated-regarding

The next Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held at 11.00 Am to 1.00Pm on 27.01.2012 at the Dean Chamber, Govt. Rajaji Hospital, Madurai. The following members of the commitee have been attended the meeting.

1. Dr.N.Vijayasankaran,M.ch(Uro.) 094-430-58793 0452-2584397	Sr.Consultant Urologist Madurai Kidney Centre, Sivagangai Road,Madurai	Chairman
2. Dr.P.K. Muthu Kumarasamy, M.D., 9843050911	Professor & H.O.D of Medical, Oncology(Retired)	Member Secretary
3. Dr.I.Meena,MD 094-437-74875	Professor of Physiology, Madurai Medical College	Member
4. Dr. S. Thamilarasi, M.D (Pharmacol)	Professor of pharmacology	
5.Dr.Moses K.Daniel MD(Gen.Medicine) 098-421-56066	Professor of Medicine Madurai Medical College	Member
6.Dr.M.Gobinath,MS(Gen.Surgery) 097-871-50040	Professor of Surgery Madurai Medical College	Member
7.Dr.S. Dilshadh, MD(O&G)	Professor of OP&Gyn Madurai Medical College	Member
8.Dr.S.Vadivel Murugan., M.D. 097-871-50040	Professor of Medicine Madurai Medical College	Member
9.Shri.M.Sridher,B.sc.B.L. 099-949-07400	Advocate, 623-B II Floor East II Cross K.K.Nagar,Madurai.20.	Member
10.Shri.O.B.D.Bharat,B.sc., 094-437-14162	Businessman Plot No.588 K.K.Nagar,Madurai.20.	Member
11.Shri. S.sivakumar,M.A(Social) Mphil 093-444-84990	Sociologist, Plot No.51 F.F, K.K. Nagar, Madurai	Member

Following Projects were approved by the committee

Sl. No	Name of P.G.	Course	Name of the Project	Remarks
1.	Anuj Saigal.	PG. M.D.(dvl)	Morphea: a clinical and histopathologic study.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance.
She/He should inform the IEC immediately, in case of any adverse events or Serious adverse reactions.
4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

DEAN 22/2

To
All the above members and Head of the Departments concerned.
All the Applicants.

MASTER CHART

NAME	NUMBER	TYPE OF MORPHOEA	AGE OF ONSET	DURATION OF LESIONS	SEX	SIDE	FOREHEAD AND SCALP	FACE	CHEST	BREAST	BACK	ABDOMEN	UPPER LIMBS	LOWER LIMBS	SYMPTOMS	EVOLUTION	PRECIPITATING FACTORS	FAMILY HISTORY	BIRTH HISTORY	ASSOCIATED SYSTEMIC DISEASES	NUMBER OF LESIONS	SENSATION	CONTRACTURES	ATROPHY	COMPLETE BLOOD COUNT	LIVER FUNCTION TESTS	X RAY	SITE OF BIOPSY	HISTOPATHOLOGY	STAGE	EPIDERMIS	DERMIS	SC TISSUE	ASSOCIATED SKIN DISEASES	NAIL CHANGES
Bindiya	1	C	17 y	7 mo	F	R							p		I	pr	N	N	NCM	N	S	n	N	N	n	n	NA	ce	co	int	At	Infl- PA	Infl	N	N
Pandeeshwari	2	C	49 y	1 mo	F	B						p	p		I	pr	N	N	NCM	N	M	n	N	N	n	n	NA	ce	co	ear	n	Infl- PA	NI	HS	N
Muthurathinam	3	C	21 y	1 y	F	B							p		I	pr	N	N	CM-2	N	M	n	N	N	n	n	NA	ce	co	int	At	Infl- PA	Infl	N	N
Johnson	4	C	51 y	6 mo	M	L		p							N	pr	Tr	N	NCM	N	S	n	N	N	n	n	NA	a) ed b) ce	co	a) ear b) int	a)n, b) n	a) Infl- PV,b) Infl-PA	a)NI,b)Infl	N	N
Kaleeshwari	5	C	12 y	3 mo	F	B					p		p		I, DC	pr	N	N	NCM	N	M	n	N	N	n	n	NA	ce	co	ear	n	Infl-PA, PV	NI	N	N
Balaji M.S	6	C	20 y	1 y	M	R		p			p				H	pr	N	N	NCM	BA	M	n	N	N	n	n	NA	ce	co	int	At	Infl-PA, PV	Infl	N	N
Ponammal Devi	7	C	47 y	3 y	F	B							p-B	p-L	N	pr	N	N	NCM	DM	M	n	N	N	n	n	NA	ce	co	int	At	Infl-PA, PV	Infl	N	N
Kavitha	8	G	7 y	13 y	F	B			p		p		p-B	p-B	I	pr	N	N	CM-3	N	M	n	N	N	n	n	NA	a) ed b) ce	co	a) int b) int	a)At,b) At	a)Infl- PV, b)Infl- PA	a)Infl, b)Infl	N	N
Priyadarshini	9	G	11 y	3 mo	F	B					p	p	p-B	p-B	N	pr	N	p	NCM	N	M	n	N	N	n	n	NA	ce	co	ear	n	Infl- PV	NI	N	N
Thangaselvi	10	L(TL)	28 y	2 y	F	B							p-B	p-L	Ar	pr	Preg	N	NCM	N	M	n	N	N	n	n	n	ce	co	ear-int	n	Infl- PV	Infl	N	N
Seetharaman	11	L(TL)	14 y	6 mo	M	R			p				p-R		N	pr	N	N	NCM	N	M	n	N	N	n	n	n	ce	co	ear	At, pig	Infl-PV	NI	N	LNY
Kanimozhi	12	C	20 y	2 mo	F	R					p				N	pr	N	N	NCM	N	S	n	N	N	n	n	NA	a) ed b) ce	co	a) ear b) ear	a)n, pigb)n	a)Infl- PV,PA b) Infl-PV	a)NI b) NI	N	N
Valli	13	G	48 y	2 y	F	B			p		p	p	p-B	p-B	Ar, H	pr	N	N	NCM	N	M	n	N	N	n	n	NA	ce	co	lat	n	NI	NI	K	MNY
Saranya	14	C	15 y	1 mo	F	L								p	N	s	N	N	NCM	N	M	VL	N	N	E	n	NA	ce	co	ear	At	Infl-PV, PA	NI	N	N
Satipriya	15	M (L-C)	11 y	6 mo	F	R						p		p	I	pr	N	N	CM- 3	N	M	n	N	N	n	n	NA	ce	co	ear	n	Infl- PA	NI	N	N
Anushya	16	C	12 y	2 mo	F	R							p		N	pr	N	N	NCM	N	S	n	N	N	A	n	NA	ce	co	ear	At	Infl-PV, PA	NI	N	N
Uma	17	PSM	19 y	5 y	F	R								p	I	s	N	N	NCM	N	M	VL	p	P-Li	n	n	Co	ce	co	int	At, pig	Infl-PA, PV	Infl	Ps	N
Rohini	18	C	6 y	1 y	F	R					p				N	s	N	N	NCM	N	S	n	N	N	n	n	NA	a)ed b) ce	co	a) ear b) int	a) At b) At	a) Infl-PV,PA b) Infl-PV,PA	a) NI b) Infl	N	N
Mousijan	19	C	7 y	1 mo	M	R					p				N	pr	N	N	NCM	N	S	n	N	N	E	n	NA	ce	co	ear	At	Infl-PV	NI	N	N
Ranji	20	C	10 y	6 mo	F	B						p	p-B	p-B	N	pr	N	N	NCM	N	M	n	N	N	E	n	NA	a) ed b) ce	co	a) ear b) int	a)At,b) At	a)Infl-PV,b)Infl-PA,PV	a)NI b) Infl	N	N
Praveen kumar	21	L(TL)	10 y	1 y	M	R								p	I	pr	N	N	NCM	N	M	n	N	N	n	n	n	a) ed b) ce	co	a) ear b) int	a)At b) At	a) Infl- PV b) Infl- PV	a) NI b) Infl	N	N
Ramuthai	22	C	7 y	1 y	F	L					p				I, H	pr	Tr	N	NCM	N	S	n	N	N	A, E	n	NA	ed	co	ear	At	Infl-PV, PA	NI	N	N
Prasanthani	23	C	7 y	3 mo	F	L								p	N	pr	N	N	NCM	N	S	n	N	N	n	n	NA	ce	co	ear	n	Infl- PA	NI	N	N
Ramya	24	C	13 y	2 mo	F	B							p-B	p-B	I	pr	N	N	CM-3	N	M	n	N	N	E	n	NA	a)ed b) ce	co	a) ear b) ear	a) At b) At	a) Infl-PV SEC b) Infl	A) NI b) NI	N	N
Anita	25	C	19 y	1 y	F	B								p-B	N	pr	N	N	NCM	N	M	n	N	N	n	n	NA	a) ed b)ce	co	a) ear b) int	a) At b) At	a) Infl- PV b)Infl- PV	a)NI b) Infl	N	N
Raja	26	L(HV-E)	32 y	1 mo	M	R	p								N	pr	N	N	NCM	N	S	n	N	N	n	n	NA	ce	co	ear	n	Infl- PV	NI	N	N
Seethalaxmi	27	L(TL)	50 y	7 mo	F	R								p	Ar	pr	N	N	NCM	DM	M	n	N	N	n	n	n	ce	co	int	At	Infl- PV	Infl	N	ND
Kritika	28	C	8 y	1 y	F	L					p				N	s	N	N	NCM	N	S	n	N	N	n	n	NA	ed	co	ear	At	Infl- PA	NI	N	N
Utchimahali	29	L(TL)	24 y	5 mo	F	R			p		p		p		I	pr	N	N	NCM	N	M	VL	N	N	n	n	n	ce	co	ear	At	Infl- PV	NI	N	N
Amrithalaxmi	30	O(K)	19 y	15 mo	F	B			p- R			p-L			N	pr	N	N	NCM	N	M	n	N	N	n	n	NA	a)ce b) ce	co	a) kel b) ear	a) n b) At	a) kel b) Infl- PV	a)NI b) NI	N	N
Veeranan	31	C	28 y	4 y	M	L					p	p			I	s	N	N	NCM	N	M	n	N	N	E	n	NA	ed	co	ear	n, pig	Infl- PV	NI	SM	N
Velumrugan	32	C	17 y	3 mo	M	L								p	N	s	N	N	NCM	N	S	n	N	N	n	n	NA	ce	co	ear	At	Infl- PV	NI	N	N
Dinesh	33	L(TL)	14 y	2 mo	M	R					p	p			I	pr	N	N	NCM	N	S	n	N	N	n	n	NA	a) ce b)ed	co	a) ear b) LSA	a) At b) LSA	a) Infl- PV b) LSA	a)NI b) LSA	BN, LSA	LNY
Venkatesh	34	L(HV-E)	14 y	4 y	M	L	p	p							DFG	r	N	N	CM-3	N	S	n	N	N	n	n	NA	ed	co	ear	At, pig	Infl- PV	NI	N	N
Jayshree	35	C	5 y	7 mo	F	R					p	p- R			N	pr	Tr	N	NCM	N	M	n	N	N	n	n	NA	ce	co	int	n	Infl- PV	Infl	N	N
Gandhimathi	36	G	47 y	1 y	F	B					p		p-B		N	pr	N	N	NCM	N	M	n	N	N	n	n	NA	ce	co	int	At	NI	Infl	N	N
Hridhya Mary	37	C	71 y	6 mo	F	B								p-B	I, Ar	pr	N	N	NCM	HT	M	n	N	N	n	n	NA	a) ed b) ce	co	a) LSA b) ear	a) LSA b) At	a) LSA b)Infl- PV	a) LSA b) NI	LSA	N
Nagarjun	38	C	18 y	4 mo	M	R					p				N	pr	N	N	NCM	N	S	n	N	N	n	n	NA	a) ed b) ce	co	a) ear b) ear	a)At b) At	a)Infl- PV b) Infl-PV	a)NI b) NI	N	N
Artika jesau	39	C	2 y 3 mo	2 mo	F	L	p								N	s	N	N	NCM	N	S	n	N	N	n	n	NA	ce	co	ear	n	Infl- PV	NI	N	N
Suganya	40	C	5 y	2 y	F	R					p				I	pr	N	N	NCM	N	S	n	N	N	n	n	NA	ed	co	ear	n	a) Infl-PV	NI	LS	N
Maadesh	41	M(L-C)	6 y	8 mo	M	L	p	p				p		p	N	pr	N	N	NCM	N	M	n	N	N	A, E	n	n	ce	co	int	At	Infl- PV	Infl	N	N
Selvi	42	L(TL)	37 y	6 mo	F	L						p	p	p	N	pr	N	N	NCM	N	M	n	N	N	E	n	n	ce	co	ear	At	Infl- PV	NI	V	N
Kaveri	43	L(TL)	26 y	1 y	F	B							p		DC	pr	N	N	NCM	N	M	n	N	N	n	n	n	a) ed b) ce	co	a) ear b) int- late	a) At b) n	a) Infl- PV b) Infl- PV	a) NI b) Infl	N	N
Shammima	44	G	30 y	5 y	F	B				p-B			p-B		DC	pr	N	N	NCM	N	M	n	N	N	A, E	n	NA	ed	co	ear	At	Infl- PV	NI	LSA, V	N
Shanti	45	C	38 y	1 y	F	L						p			I, DC	s	Tr	N	CM-3	N	S	n	N	N	A	n	NA	ed	co	ear	At	Infl-PA, PV	NI	N	N
Selvi	46	L(TL)	27 y	2 y	F	B							p-B	p-B	RP	pr	N	N	NCM	N	M	n	N	N	n	n	n	ce	co	int	n	NI	Infl	N	N
Muthumari	47	L(TL)	32 y	7 mo	F	R						p	p		I	pr	N	N	CM-2	N	M	n	N	N	n	n	n	ce	co	int	At	Infl-PV	Infl	N	N
Gangashree	48	C	3 y	1 y	F	R					p				I	pr	N	N	NCM	N	S	n	N	N	n	n	NA	ce	co	int	At	Infl- PV	Infl	N	N
Kalaivani	49	L(HV-P)	18y	2 y	F	L		p							DC,DFG	pr	N	N	NCM	N	M	n	N	HA-F	n	n	n	ce	co	int	At	Infl- PV	Infl	CM	N
Thangam	50	C	17 y	15 y	F	R							p		DC	pr	N	N	NCM	N	M	n	N	N	n	Abn	NA	ce	co	lat	n	NI	NI	N	N
Veeralaxmi	51	L(TL)	7 y	6 y	F	B					p		p-B		DC,I	pr	N	N	CM-2	N	M	n	N	N	n	n	a) ce b)ce	co	a) lat b) LSA	a) At b) LSA	a) NIb) LSA	a) NI b) LSA	LSA	N
Aarthi	52	L(HV-E)	14 y	6y	F	B	p								N	pr	N	N	NCM	N	M	n	N	N	A,E	n	n	ce	co	lat	At	NI	Infl	N	N
Bose	53	PSM	13 y	25 y	M	B							p-B	p-R	DC,DFG	s	N	N	NCM	N	M	n	p	p-Li, HA-T	n	n	Co	ce	co	lat	At	NI	NI	N	N
Chinnasamy	54	PSM	14 y	22 y	M	B							p-B	p-B	DC,DFG	s	N	N	CM-3	HT	M	n	p	HA-T	n	n	Co	ce	co	lat	n	NI	NI	N	ND

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